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A SYNDROME RESEMBLING PROGERIA: A REVIEW OF TWO CASES

BY

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From the Queen Elizabeth Hospital for Children, London

(RECEIVED FOR PUBLICATION JULY 29, 1949)

We are presenting two cases, which we consider to be examples of a syndrome allied to progeria, in some detail because no exactly similar cases appear to have been recorded.

These children were first seen at the Queen Elizabeth Hospital, Hackney, by Dr. Helen Mackay in June, 1947. They present strikingly similar clinical pictures, the outstanding features being dwarfism, microcephaly, a fine diffuse characteristic 'pepper and salt' choroido-retinitis, and intracranial calcification. The elder (A.P.) has recently developed deafness. They are both mentally defective. Their characteristic posture can be seen in Fig. 1, and Fig. 2 shows them compared with their normal sister.

Family History

The family history is essentially unrevealing but is shown in as much detail as is obtainable.

History of A.P.

A.P., aged 16 years, the older and the more severely affected of the two, has been examined more frequently than his brother and has several times been admitted to other hospitals. He was born at home on March 7, 1933, following a normal pregnancy and labour and weighed 7½ lb. at birth. He was breast fed for seven months and seemed normal in early infancy. The mother is uncertain of his early milestones, but by 13 months he could crawl and sit up and say a few simple words. He cut his first tooth at over one year, fed himself at 16 months, and started to walk at 2½ years. The mother thinks he gained weight normally during the first year, but he was taken to Great Ormond Street Hospital at 13 months on account of inability to walk and his condition was then diagnosed as infantilism. Thereafter he failed to grow normally and his mother thinks he is now smaller in the face and thinner than he was at 5 years old, and that his speech is less distinct and he talks less than at 7 years old.

Tremor was first noted when the child was 2 to 3 years old, and has persisted ever since, becoming more gross in the past year. His gait has always been unsteady, and he has fallen easily, especially in the past year.

When 6 years old (in 1939) he was admitted to the Queen Elizabeth Hospital, Shadwell, under Dr. O'Reilly, for failure to grow and backwardness in speech. His weight was 23¾ lb.; height 37 in.; span 36 in. He had a coarse tremor described as of 'intention type'; he was said to look 'rather elderly'; and his hands and feet were relatively large; there was some pigmentation of the skin of the face, which was dry and wrinkled. He was microcephalic (head circumference 17¼ in.), and already showed a tendency to valgus deformity of feet. A

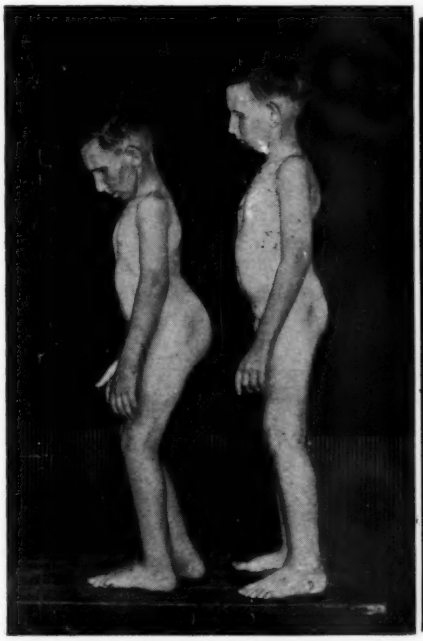
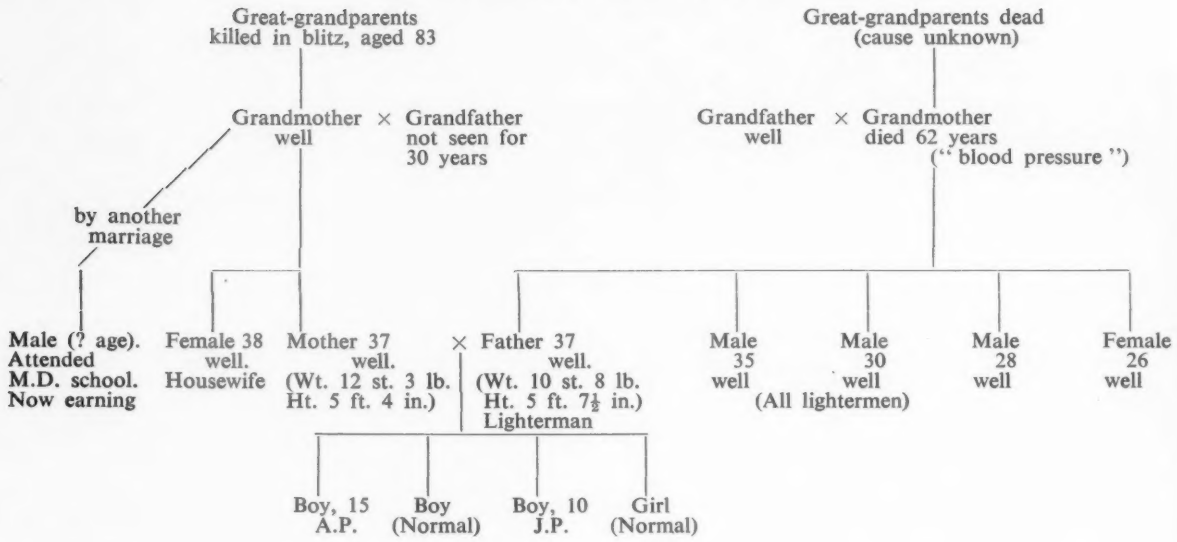


FIG. 1.—Characteristic posture.

FIG. 2.—A.P. and J.P. compared with their normal sister.

GENEALOGICAL TABLE OF P. FAMILY



radiograph of the skull showed calcification, which was thought to be a calcified haemangioma. He was given some gonadal injections for undescended testes with no effect.

There is no note on his ocular fundi.

At 8 years old (in 1941) A.P. was medically examined and classified as ineducable. His defective articulation, insecure gait, and 'old man' appearance with sunken eyes were remarked on. He could use only a few short phrases, and could not count or read at all or copy signs. His mental age was assessed as 3 years 4 months.

His weight was 26 lb., his height 36½ in., and his head circumference 17 in. (Dr. Forbes).

At 12½ years (December, 1945) he was admitted to the West End Hospital for Nervous Diseases (Dr. Simpson). He was noted to be slightly deaf, and to have carious teeth, in addition to the points previously noted. The cerebrospinal fluid contained 13 cells per c.mm. (lymphocytes 96%) and 100 mg. protein. A radiograph of the skull showed trabecular calcification in both hemispheres, in the choroid plexus, and in frontal and parietal cortex.

When 15 years old (January, 1948) he was admitted to the Queen Elizabeth Hospital, Hackney, and the findings there are given below. He had been having fairly frequent pains in his legs and was falling more frequently. He was sometimes incontinent. Since his discharge in March, 1948, he has become quieter and more miserable with a frequent cough; he is now persistently incontinent. His deafness is now almost complete. He can still see near objects fairly well.

He has had measles, pertussis, chickenpox, pneumonia, and jaundice (four years ago).

History of J.P.

J.P., aged 11 years, was born on April 7, 1938. Pregnancy and labour were normal, and the birth weight was 8 lb. Infancy was normal. The first tooth appeared at over 12 months. He walked when he was about 2½ years old and his gait has always been unsteady. Tremor has been less severe than that of A.P., but has become more marked recently. His own doctor said when the child was 2½ years old that he would be like his brother A.P. He has, however, grown rather better than A.P., and remains larger and less microcephalic.

He was medically examined at 3 years and found to be 'undersized and shrunken,' with unsteady gait, gross tremor, and defective articulation. He was dry during the day; his large prominent ears were commented on. At 4½ years he showed excessive salivation, but this was much less by 7 years and is now not troublesome. Dental caries was marked by 6 years. His mental age at 7 years was assessed at less than 3 years. No radiographs of the skull were taken, nor comment made on the ocular fundi.

When 9¾ years old he was admitted to the Queen Elizabeth Hospital, Hackney, and the findings there are given below. Since discharge in March, 1948, he has shown little change: his hearing is probably somewhat impaired. He is now more frequently incontinent than he was a year ago.

He has had measles, pertussis, scarlet fever, and pneumonia (two attacks).

Clinical Examinations

A.P. is of very small stature, the trunk particularly small, and the extremities relatively large. The legs appear long. There is lumbar lordosis, a slightly protuberant abdomen, pes valgus, and a fixed flexion deformity (10°) of the knees. His gait is 'tottering' and he falls fairly frequently. A coarse tremor (intentional type) is present. Pigmented moles are numerous on the head and neck, arms and legs. The child is microcephalic (i.e. head circumference small but *no* sloping of forehead), with prominent ears and sunken eyeballs. The skin of the face is stretched and shows some wrinkling, but elsewhere is of normal texture, although it is

rough and rather dry on the hands and feet. The hair is dry and thin and a little scanty. The eyebrows and lashes are normal (Fig. 3).

FIG. 3.—Photograph of A.P.

CARDIOVASCULAR SYSTEM. No arteriosclerosis in January, 1948, but by November, 1948, shows definite arterial thickening. Heart not enlarged. Aortic second sound accentuated. Blood pressure 120/70.

RESPIRATORY SYSTEM. Normal; chest expansion slight.

DIGESTIVE SYSTEM. Teeth irregular, grossly carious, some missing (see x-ray reports). Gums hypertrophied.

ABDOMEN. In January, 1948, liver enlarged one finger below costal margin (increased to two and a half fingers by November, 1948). Spleen enlarged two fingers below costal margin.

UROGENITAL SYSTEM. Bilateral undescended testes. No secondary sex characteristics.

CENTRAL NERVOUS SYSTEM. Pupils slightly irregular; very small; react *very* slightly to light and accommodation; very slow response to mydriatics. Other cranial nerves appear normal, apart from rapidly increasing deafness for past year now almost complete. Limbs stiff but not definitely spastic. Jerks brisk. Plantars flexor.

Fundi show 'degenerative retinitis of the pepper and salt type. Advanced optic atrophy both eyes.' (Mr. J. Minton, F.R.C.S.)

J.P. The clinical picture is in general very similar to that of A.P. J.P. is less severely affected (Figs. 1 and 2). He is slightly taller, and looks paler, with less wrinkling and pigmentation. His ears are more prominent. His posture is less abnormal.

The spleen is only just palpable; liver one finger-breadth; blood pressure 112/60. No evidence of arteriosclerosis. Teeth less carious. Optic atrophy less marked but retinae similar.

Measurements

The children were measured in January, 1948, and their measurements compared with those of their normal brother aged 13 years (Table 1).

Re-measuring in November, 1948, showed a slight decrease in A.P.'s height (2 in.) probably due to increased lordosis and flexion.

Laboratory Investigations

Blood. Full laboratory investigations were made in January, 1948, and the results are set out as follows (Tables 2 and 3).

Toxoplasmosis Tests.—Dr. Sven Gaard (Stockholm) tested the serum of A.P. and Mrs. P. for toxoplasma

TABLE 1
MEASUREMENTS OF A.P. AND J.P. COMPARED WITH THOSE OF THEIR NORMAL BROTHER

	A.P.	J.P.	Normal brother
Weight	30 lb. 5 oz.	34 lb. 14 oz.	
Height*	40½ in.	44 in.	57 in.
Sitting height	21 in.	24¼ in.	
Upper measurement (crown-symphysis)	18 in.	19¾ in.	
Lower measurement (symphysis-sole)	21¼ in.	22½ in.	28¼ in.
	(R. and L.)	(R. and L.)	
Ratio upper: lower measurement	0·85	0·87	
Head circumference	18 in.	19⅜ in.	
Chest circumference	19½ in.	21¼ in.	
Girth (round umbilicus)	20½ in.	21½ in.	
Width (intercristal)	9½ in.	9¼ in.	
Girth of arm (biceps) 2 in. above olecranon (flexed and extended)	6½ in.	6¾ in.	
	(R. and L.)	(R. and L.)	
Span	38⅝ in.	42⅝ in.	59 in.
Length of arm	14⅝ in.	16⅛ in.	
Length of foot	7 in.	7 in.	
	(R. and L.)	(R. and L.)	

* Measurements of height, etc., are approximate only, as the lordosis and fixed flexion of the knees make complete accuracy impossible.

TABLE 2

RESULTS OF LABORATORY INVESTIGATIONS

	A.P.	J.P.
Hb.	92%	96%
R.B.C.s	4,750,000	5,000,000
W.B.C.s	8,400	12,000
	(P. 54%; E. 2%; L. 42%; M. 2%)	(P. 61%; E. 3%; L. 32%; M. 4%)
Wassermann and Kahn tests	Negative	Negative
Tuberculin (jelly test)	Negative	Negative
Serum potassium level	22·4 mg. %	21·4 mg. %
Serum phosphate level	3·37 mg. %	3·72 mg. %
Serum phosphatase level	17·4 units	15·3 units
Serum calcium level	10·0 mg. %	9·9 mg. %
Serum cholesterol level	195 mg. %	240 mg. %
Serum protein level	6·92	6·10
	(Albumin, 4·99; Globulin, 1·93)	(Albumin, 4·86; Globulin, 1·24)
Serum chlorides	600 mg. %	588 mg. %
Serum sodium	344 mg. %	344 mg. %
Blood urea	38 mg. %	44 mg. %
Urea clearance	83% of normal	78% of normal
Thymol turbidity	4 units	4 units
Non-protein nitrogen level	41 mg. %	50 mg. %
Urine	Acid (yellow). Protein: very faint trace. Sugar: nil. Deposit: n.a.d.	Acid (yellow). Protein: nil. Sugar: nil. Deposit: n.a.d.
Urinary amino-acid nitrogen	44 mg./100 ml.	94 mg./100 ml.
	(Both within normal limits)	
Urinary 17-ketosteroids (Dr. Patterson, Charing Cross Hospital)	2·0 mg./24 hours	1·1 mg./24 hours
	(Both low values)	

TAPLE 3

SUGAR TOLERANCE TEST (1¾ g./kg.)

	A.P.		J.P.	
		Urine		Urine
Fasting	70 mg. %		84 mg. %	
½ hour	200 mg. %	Nil	204 mg. %	Nil
1 hour	195 mg. %		191 mg. %	
1½ hours	79 mg. %	Sugar +	66 mg. %	Sugar +
2 hours	43 mg. %		52 mg. %	
Basal metabolic rate (Dr. C. Pillman Williams, Royal Free Hospital)	−17·5 (calculated on weight and/or on age)		−47·5 (unsatisfactory test)	

antibodies. That of A.P. was negative, and that of the mother gave a titre of 1:40 which is not significant.

Tests for toxoplasmosis were also made at the Hospital for Sick Children, Great Ormond Street, by Dr. J. A. Dudgeon and Dr. I. A. B. Cathie on J.P., A.P., M.P. (sister), and Mrs. P. (mother). Their report is as follows (April 13, 1950).

NEUTRALIZATION TEST (SABIN, 1942). The results on all four members of the family were negative.

COMPLEMENT FIXATION TEST (SABIN, 1949). The results on all four members of the family were negative, using a purified antigen as suggested by Sabin.

TOXOPLASMIN SKIN TEST (FRENKEL, 1948). The results on all four members of the family were negative at 1/100.

DYE TEST (SABIN AND FELDMAN, 1948). This test was negative on J.P. and A.P. and positive at 1/16 on M.P. and Mrs. P. In our experience such titres do not appear to be significant.

Urinary amino-acids on chromatographic separation show no abnormality.

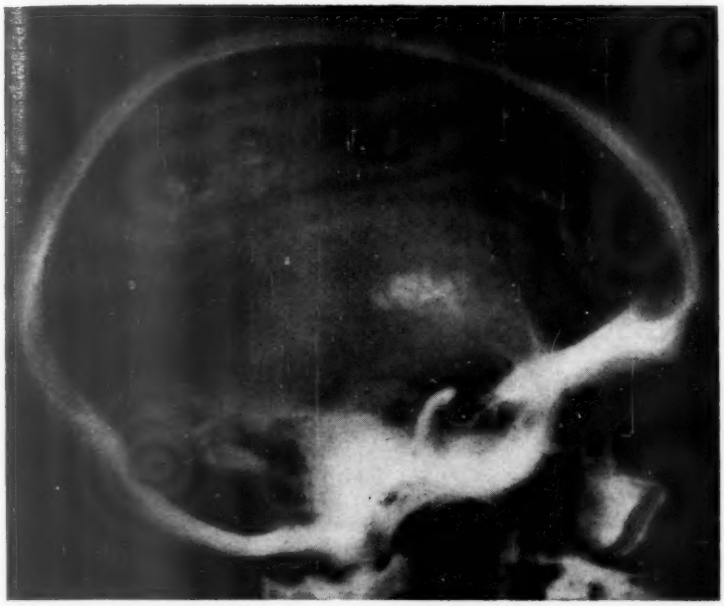


FIG. 4.—Lateral radiograph of skull of A.P., showing distribution of calcification.

Radiological Investigations

A.P. 'The skull as a whole is small, normally proportioned and with a thick calvarium. There are several scattered areas of calcification whose exact siting depends on the relation of the ventricular systems to the actual brain tissue. There is some evidence that the former may be dilated.

There are three main areas of calcification: (1) Two bilateral disc-shaped areas of mottling lying just lateral to the anterior horns of the lateral ventricles, presuming these are normal in size and position; (2) bilateral calcification apparently in the dorsum sellae and tentorium cerebelli regions; (3) bilateral calcification in the lateral, frontal, and middle parietal regions which is probably near the surface of the skull and may actually be in the cortex or meninges. Its distribution suggests that it follows the cerebral convolutions. Thus each area of calcification could conceivably lie in the meninges or the walls of dilated ventricles.

The sella turcica is normal.'

'The bones as a whole are smaller and more slender than usually found in this child's age group. There is slight general osteoporosis of the extremities. The bone age is within normal limits, however. There is well marked differentiation between cortex and medulla and the only structural abnormality apart from their size is a slight generalized coarseness of the trabeculae.'

DENTITION.—'Left lower 6 and right lower 6 roots are present and show chronic apical abscesses. Upper left 6, 4, 3, and upper right 3 show advanced dental caries. Upper left 4 is unerupted. Upper left 2 and 1 and upper right 1 and 2 have been extracted. The state of the dentition is normal for a boy aged 15.'

J.P. 'General appearance of the skull is similar to that of A.P. and the calcification appears to be in similar positions but is less gross.'

Bones show essentially similar changes to those of A.P.' (Dr. C. J. Hodson.)

DENTITION.—Upper right 5 and upper left 5 are absent. Upper left c and upper right c and lower left c and lower right c, d, and e are the only deciduous teeth present and they have complete root absorption. No evidence of periapical infection. The state of the dentition is within normal limits for a boy of 10 years.

Mental State

Intelligence tests were given to all four children in this family.

The second and fourth child (boy and girl) are of average intelligence according to the test results (boy aged 13 years 11 months: I.Q. 106; girl aged 7 years 8 months: I.Q. 109).

A.P., whose chronological age is 15 years, has a mental age of 2 years 3 months. This was established by the Merrill Palmer test (2 years 3 months); the revised Stanford Binet test (2 years 3 months); and Gesell's norms (2 years 5 months).

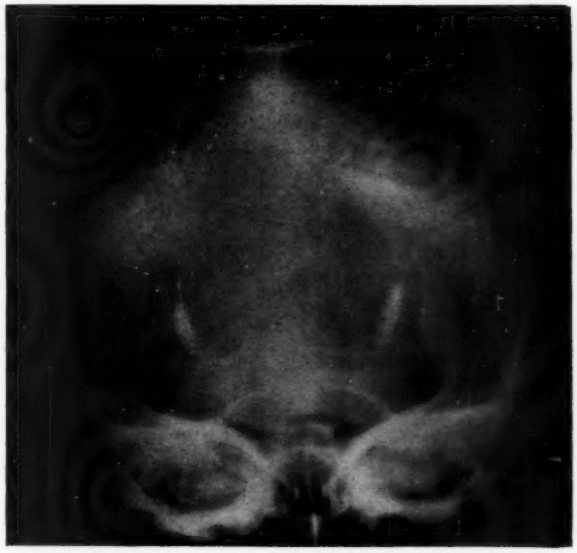


FIG. 5.—Antero-posterior view of skull of A.P.

J.P., whose chronological age is 9 years 11 months, has a mental age of almost 2½ years, the three tests showing a difference of one month (Merrill Palmer, 2 years 5 months; revised Stanford Binet, 2 years 4 months; Gesell's norms, 2 years 6 months).

Both children are classifiable as idiot. J.P. makes a slightly higher score than A.P. A.P.'s intelligence may have regressed a little in the last few years. There are some indications that both children have regressed since first tested in June, 1947. This may be due to their period in hospital, and be temporary, or it may be an actual lessening of intellectual ability. The parents and teachers support the latter view.

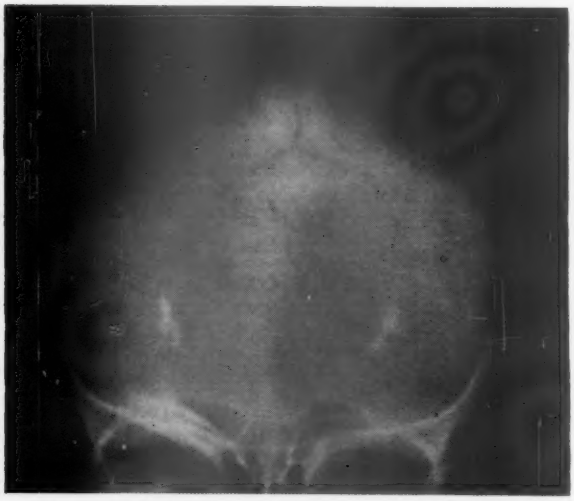


FIG. 6.—Antero-posterior view of skull of J.P.

Although both children are idiots their behaviour is unlike that of idiots of their age. Both children play very like normal 2-2½ year-olds, except that they cannot rush wildly around, but they have all the joviality, warm human affections and interest in life of the typical 2-3 year-old. They can be very jealous. One makes a much closer contact with them than one usually does with idiots and imbeciles, or possibly even high grade defectives of their chronological age. Their social adaptation is very good and this accounts for the slightly higher score achieved by both on Gesell's norms. This good social adaptation may be due to the fact that there are two of them; to the parents who have made a united affectionate family out of some oddly assorted children; the idiocy appears to be secondary and so the impulse to grow and develop would be stronger in the first few years than in cases of primary idiocy. In contrast to their general emotional reactions which are on the 2½ year-old level their hand movements are almost adult. This is probably due to practice and maturation.

There is an obvious difference in personality between the two children. A.P. is the more forthcoming, the extrovert; J.P. is silent and retiring, the introvert.

The detailed results of intelligence tests are appended for future comparison with any similar case.

During the past year (January, 1948, to January, 1949) A.P. has developed definite arteriosclerosis, and is undoubtedly becoming weaker and less happy; he has also become almost completely deaf and completely incontinent. He has frequent coughs and bronchitis and is generally frailer.

He has had one or two attacks of loss of consciousness but no definite convulsions. There have been no anginal attacks.

J.P. has shown little change apart from increasing incontinence. His eyes are rather more sunken but his weight is being maintained. There is probably slight difficulty in hearing but nothing approaching complete deafness.

Discussion

The outstanding clinical features of these two brothers appear to be (1) the similarity to each other, and difference from the rest of the family; (2) the appearance, which is a compound of dwarfism and apparent senility, an exceptionally small trunk with disproportionately longer extremities, a very small head (not showing the usual stigmata of microcephaly), a characteristic posture, a coarse intention tremor, and a rather tottering gait. They show some pigmentation, which is not gross, some loss of subcutaneous fat, most marked on the face, and a gross degree of sexual infantilism; (3) the degenerative retinitis with fine, widespread pigmentation over the whole fundus, and a fairly advanced optic atrophy. The appearance is exactly similar to that of Cockayne's cases (1936); (4) the intracranial calcification, which is extensive, situated chiefly in the neighbourhood of the choroid plexuses but also in the frontal region; (5) the apparent hepatomegaly in both, and the splenomegaly in the older child only; (6) the idiocy.

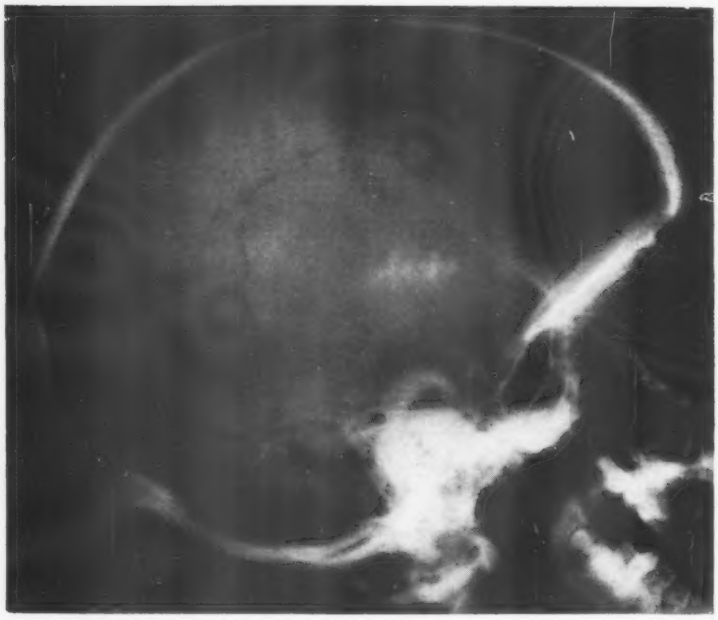


FIG. 7.—Lateral radiograph of skull of J.P. showing less extensive calcification.

These features do not appear to fit into any well-defined syndrome, but the two brothers show a marked resemblance to two cases published by Cockayne in 1936 and re-described in 1946 as

Dwarfism with Retinal Atrophy and Deafness. These patients were a brother and sister, aged respectively 6 and 7 years in 1936, two of seven siblings all the rest being normal. They were grossly dwarfed, underweight, with small heads similar in shape to those of the two patients described. They showed an exactly similar type of retinal degeneration: his two cases were greatly mentally retarded, but their mentality was difficult to assess. By 1946 both were blind from optic atrophy, and had bilateral cataracts. They were also by this time completely deaf, having been only slightly deaf in 1936. Cockayne found no reference to previous similar cases, and discusses the differences between his cases and retinitis pigmentosa. He states that the type of pigmentation is essentially finer and more diffuse than in retinitis pigmentosa and there are none of the large 'bone corpuscle' deposits of pigment characteristic of the latter condition. And although retinitis pigmentosa may be associated with deafness, epilepsy and mental deterioration, it has never been recorded associated with dwarfism and microcephaly. His cases differ from ours in having cataracts, and in the absence of intracranial calcification and of hepatosplenomegaly; but despite these considerable differences, there seems little doubt that they are essentially the same condition. Cockayne did not comment on any possible relationship between his cases and progeria, but there are some important similarities.

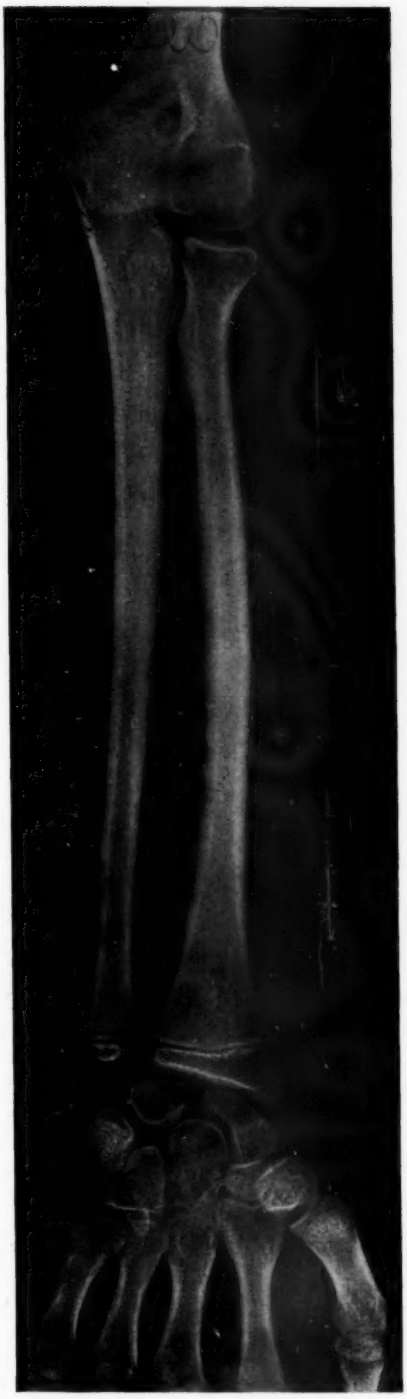


FIG. 8.—Radius and ulna of A.P.

Progeria was first described by Hutchinson in 1886. Gilford in 1904 re-described Hutchinson's case, who had by that time died at the age of 17 years, and gave another case of his own. He originally called the condition micromegaly (because of the contrasts it presented to acromegaly), but later called it progeria. Since then about 20 classical cases have been described, and a number of others showing similarities but not completely typical. The classical picture is well shown in a photograph of Gilford's case (Thomson and Forfar, 1950; see Fig. 2, p. 224.)

The essential features are dwarfism, loss of hair, an old appearance, loss of subcutaneous fat, a dry stretched skin showing some wrinkling, arthritis producing the typical posture, osteoporosis, and arteriosclerosis. The last named is the usual cause of death, which may occur from coronary disease or a cerebral vascular accident before the age of 20. The mentality is usually said to be normal or slightly low, but there are no gross mental defectives among the classical cases. Our two cases show the following points in common with progeria: (1) onset of dwarfism at about one year of age; (2) senile appearance; (3) mild arthritis; (4) osteoporosis; (5) stretching of the skin of the face and some pigmentation of the skin; (6) calcification of blood vessels. They differ from progeria in (1) their gross mental deficiency; (2) microcephaly, the head circumference in progeria being smaller than normal for the age, but relatively large for the size of the body; (3) retinal degeneration; (4) disproportionate size of extremities; (5) intracranial calcification; and (6) the presence of hair. Baldness is the rule in the classical cases, but is not an essential feature, and there are, for instance, two cases of Schondel's (1943) where hair was present though rather scanty; Schondel's two cases also showed microphthalmos, in contrast to the usual slightly exophthalmic picture. Her article contains an excellent review of the literature and divides the described cases into classical and atypical.

In one or two points, such as their slightly abnormal sugar tolerance and the presence of

calcification of the blood vessels our two cases resemble Werner's syndrome or 'progeria of the adult.'

We have attempted to show the points of differential diagnosis in the following chart, amended slightly from Thannhauser (1945).

Another condition that needs to be considered is toxoplasmosis. The intracranial calcification is coarser and more diffuse in our two cases than that usually described and the retinal changes are not characteristic. The serological reactions do not support the diagnosis. It is also difficult to envisage any maternal infection producing this particular family distribution of disease.

The most probable theory seems to be that the two dwarfs represent a multiple germ plasm defect, similar to that of progeria, possibly caused by a recessive gene and producing secondary extensive endocrine and metabolic disorders.

Summary

Two microcephalic dwarf brothers are described, with details of the physical and psychological investigations.

Reasons are advanced for suggesting that they are cases of multiple germ plasm defect, probably due to a recessive gene, and that this condition is allied to progeria.

TABLE 4

CLINICAL FEATURES OF VARIOUS 'MULTIPLE GERM-PHASE DEFECT' DISEASES

	Werner's Syndrome	Rothmund's Syndrome	Progeria	Cockayne's Cases	A.P. and J.P.
Familial	+ + +	+ + +	o	+	+
Age onset	20-30 (years)	3 months-30 years	2-5 (months)	1 year	? 1 year
Consanguinity	+	+	o	?	o
Short stature	+ + +	+	+ + + +	+ + + +	+ + +
Skin changes	+ + + +	+ + + +	+	+ +	+
(*a*) Tightly drawn over tissue	+ + + +	o	+	face only	face only
(*b*) Thin and atrophic	+ + + +	+ +	+ +	o	?
(*c*) Telangiectases	+	+ + 3 months	o	o	o
(*d*) Scaling	+ +	+ + + +	+	+ (hands and feet)	
(*e*) Pigmentation and depigmentation	+	+ + +	+	+ (moles)	+ (moles)
(*f*) Ulcers	+ + + + (−gangrene)	o	o	o	o
(*g*) Wrinkling and pre-senile	+	o	+ + +	o	+
Falling hair	+ + + + (age 20-30 years)	+ (age 40 years)	+ + + + (age 2-5 months)	o	(+)
Loss subcutaneous fat	+ + +	±	+ + +	+ (face)	+ (face)
Cataracts	+ + + + (age 20-30 years)	+ + + + (age 3-4 years)	o	+ + + (age 15 years)	o
Muscle atrophy distal parts	+ + +	±	+ + +	?	??
Osteoporosis	+ + +	o	+ +	o	+ +
Joint deformity	+ + +	+	+ + +	+	+
Intracranial calcification	o	o	o	o	+ + +
Sexual retardation	+ + + +	+ +	+ + +	+	+ + + +
Scanty sex hairs	+ + +	+ +	+ + +	+	+ + + +
Thyroid enlargement	+	o	o	o	o
Proptosis	+ + +	o	+ + + +	o	o
Arteriosclerosis	+ + +	±	+ + + +	(1) ? retinal (2) ? coronary attack	+ + (A.P. only)
Calcification blood vessels	+ + + (skin vessels)	o	+	o	+ + + (intracranial)
Vocal cords	+ may be "hoarse and high pitched"	o	o (high pitched voice)	?	? slightly hoarse
Pigmentation retina	o	o	o	+ + + +	+ + + +
Optic atrophy	o	o	o	+ + + +	+ + +
Asymmetry fingers	(+)		o	+	+
Splenomegaly and hepatomegaly	o	o	o	o	+
Diabetic tendency	+	o	o	o Blood sugar curve normal	+
Deafness	o	o	o	+ +	+
Microcephaly	o	o	o	+ + +	+ + +
Mental deficiency	o	o	o	+ +	+ + + +

We are most grateful to Dr. Helen Mackay for allowing us to publish these two cases, and for her stimulus and encouragement, and to Dr. B. Levin for the investigations he has carried out. We are also very grateful to Dr. Wyndham Pearce for the interest he has shown, and we should like to thank all those mentioned in the article who have made special investigations for us.

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APPENDIX

The Merril Palmer and Binet intelligence scales are tests of mixed type and many of the test items at the low age levels (i.e. under 5) are performance tests. Some test items are pass or fail: others are measured in both speed and accuracy.

Gesell's test uses norms of development based on studies of many young children, and the way in which they walk, talk, handle materials, etc. at different age levels,

The three tests were used for the sake of accuracy as well as interest. Only those items in which A.P. and J.P. were successful have been recorded here.

MERRIL-PALMER SCALE: TEST ANALYSIS

	A.P.	J.P.
Date examined	January 1, 1948	January 1, 1948
Chronological age	14 years 10 months	9 years 9 months
Mental age	2 years 5 months	2 years 5 months
Score	18	23
	Test	**Test**
18 to 23 months	Throwing ball Straight tower Questions Wallin peg board A Walking block Crossing feet Sixteen cubes Repetition of words Standing on one foot	Commands Throwing ball Straight tower Questions Wallin peg board A Walking block Crossing feet Sixteen cubes Repetition of words Folding paper
24 to 29 months	Sixteen cubes Wallin peg board A Drawing up string Cutting with scissors	Identification of self in mirror Sixteen cubes Wallin peg board A Drawing up string Nest of cubes Cutting with scissors
30 to 35 months	One button Three cube pyramid	Sixteen cubes Three cube pyramid Nest of cubes Closing fist and moving thumbs
36 to 41 months	Copying circle Little pink tower Three cube pyramid	Copying circle Three cube pyramid
42 to 47 months	—	Three cube pyramid

REVISED STANFORD BINET INTELLIGENCE SCALE (FORM L): TEST ANALYSIS

	A.P.	J.P.
Date examined	February 26, 1948	January 6, 1948
Chronological age	15 years	9 years 9 months
Mental age	2 years 3 months	2 years 4 months
Intelligence quotient	14 (idiot)	24 (idiot)
	Test	**Test**
2 years	Formboard Identification by name (4) Block tower Picture vocabulary (5) Word combination Simple commands — 100% passed	Formboard Identification by name Parts of body Picture vocabulary (5) Word combination Simple commands — 100% passed
2½ years	Naming objects (4) — 17% passed	Parts of body Identification by name — 34% passed
3 years	Stringing beads Circle — 34% passed	Stringing beads Block bridge — 34% passed

GESELL'S NORMS : TEST ANALYSIS

	A.P.	J.P.
Chronological age	14 years 10 months	9 years 9 months
Mental age (approximately) ..	2 years 5 months	2 years 5 months
	Test	**Test**
24 months	Runs (unsteadily) Kicks ball Builds tower of bricks (6) Repeats 3-4 word sentences Places blocks on form board Aligns bricks Uses 3-word sentence Names 7-picture cards Names two test objects Can control spoon in feeding Asks for toilet Pulls on, or up, a simple garment Communicates immediate experience Can ask for ' another ' Plays with several cubes at once Mimics domestic life Usually plays by himself, but has much more social contact than one would expect	Passed exactly the same test items as his brother A.P.
30 months	Can walk on tip toe very unsteadily Jumps with both feet Tries to stand on one foot Holds pencil by fingers Identifies seven picture cards Helps to put things away (if asked)	
36 months	Imitates bridge with blocks Copies circle Names eight picture cards	

PROGERIA (HUTCHINSON-GILFORD SYNDROME)

REPORT OF A CASE AND REVIEW OF THE LITERATURE

BY

JAMES THOMSON and JOHN O. FORFAR

From the Department of Medical Diseases of Children, University of St. Andrews and Royal Infirmary, Dundee

(RECEIVED FOR PUBLICATION JANUARY 24, 1950)

. . . the poor little boy didn't live to contrive,
His health didn't thrive,
No longer alive,
He died an enfeebled old dotard at five.
W. S. GILBERT (1869).

The first case of progeria to be described in medical literature was that of Hutchinson in 1886, under the title of ' Congenital Absence of Hair and Mammary Glands.' Hastings Gilford (1897) recognizing the condition as a clinical entity, described a case of his own (Figs. 1 and 2) and redescribed Hutchinson's original case. He introduced the term progeria (πρόγρος ; prematurely old). There is a tendency to use this term in connexion with other forms of early senility both in children and in adults but we agree with Crooke (1948) that it should be reserved for the specific syndrome first described by Hutchinson and Gilford.

Gilford considered it likely that a description of this syndrome would lead to the more frequent recognition of other cases and that it might be much more common than supposed. This opinion has not been borne out because we find that there has been no typical case of progeria reported in British literature since the original two cases, although Parsons (1949) and Ebbs (1949) have referred to a case and Keith (1913) has described a typical progerian skull. Cases have, however, been described in foreign literature and the outstanding feature of these descriptions is the striking similarity in appearance which all typical cases present. Variot and Pironneau (1910), unaware of Gilford's work, used the term *nanisme senile* in describing their case. A case described by Schippers (1916) was redescribed by Manschot (1940) 24 years later.

FIG. 1—Gilford's case aged 7 years.

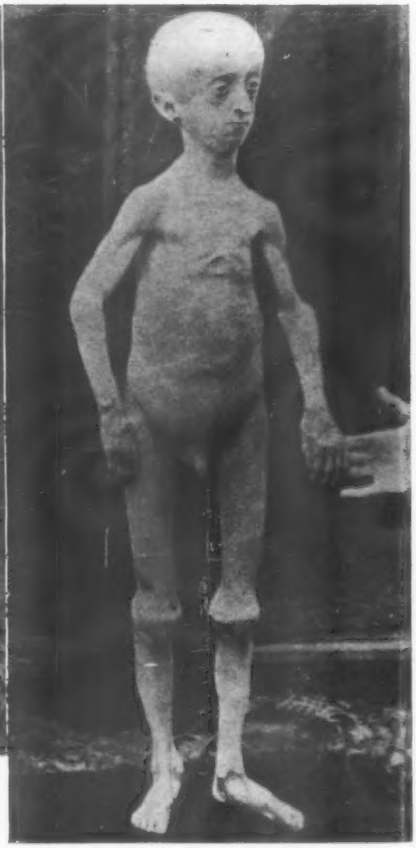

FIG. 2—Gilford's case aged 17 years.

TABLE 1

TYPICAL CASES OF PROGERIA RECORDED IN THE LITERATURE

		Sex	Age (years)	Weight (kg.)	% of Expected Weight	Height (cm.)	% of Expected Height	Age at Death	Necropsy
1	Hutchinson (1886) and Gilford (1897)	M.	15	17·2	33	109	67	17	
2	Gilford (1897)	M.	14	16·3	36	104	66	18	×
3	Variot and Pironneau (1910)	F.	15	11·6	23	102	64	15	
4	Schippers (1916) .. .. Manschot (1940)	M.	4 26	11·3 15·6	66 26	84 115	81 67	26	×
5	Oricco (1918) and Orrico and Strada (1927)	M.	19	15·4	26	113	66	21	×
6	Nasso (1925)	F.	4½			83	81		
7	Curtin and Kotzen (1929) ..	F.	7	11·7	54	96	80	9	
8	Strunz (1929)	F.	6½	9·4	45	90	77		
9	Thiers and Nahan (1933) ..	M.	19	23·2	39	131	77		
10	Schiff (1934)	F.	6½	=4 yrs. (16·6)	(79)	=4 yrs. (100)	(86)		
11	Exchaquet (1935b)	F.	14	12·9	28	113	73		
12	Broc *et al.* (1935)	M.	11	14·0	42	116	82		
13	Popek and Hadlik (1938) ..	F.	8	11·2	45	99	82		
14	Mitchell and Goltman (1940)	F.	10	12·7	42	105	78		
15	Zeder (1940)	M.	5	7·6	41	83	76		
16	Schondel (1943)	F.	5½	10·9	57	93	83		
17	Talbot *et al.* (1945)	M.	6	10·9	51	95	81	7	×
18	Schwartz and Cooke (1945)	M.	5	9·8	53	83	76		

Only 18 typical cases have so far been reported and these are enumerated in Table 1.

The cases described by Rand (1914), Lereboullet (1917), Farran-Ridge (1921), Paterson (1922), Talbot (1923), Harris (1927), Apert and Robin (1927), Apert (1933), Stoia and Andreoiu (1928), Halle and Odinet (1932), Pouzin-Malègue and Barraud (1932, 1934), Martinez (1935), Heuyer, Denoyelle, and Bernard (1936), Stern and Lieberman (1937), Schachter-Nancy (1938), Sundblad (1938), Korsgaard (1940), Müller-Hess (1940), Gottron (1940), Schondel (1942—second case), Nery (1944), Moehlig (1946), van Bolhuis (1948), and Wiedemann (1948) are not in our opinion typical cases of progeria.

Most of these cases show, however, some of the manifestations of progeria but all of them lack some of the characteristic features of typical cases. The clinical picture in progeria is so clear cut that we do not feel justified in including such variants in it. It may be that whereas progeria represents a total pathological lesion some of these atypical cases represent a partial lesion of the same nature or that in other cases the clinical picture has been modified by the occurrence at a later age period of the pathological processes responsible for progeria. Gilford (1911a) has described a possible case modified in this way by later age of onset. Gorter (1942) in describing a boy showing some of the signs of progeria, but lacking others, has suggested that the term progeroid be applied to cases of this type, that of progeria being reserved for classical cases. There seem to be good grounds for making

a distinction and grouping of this sort. Waldorp and del Castillo (1928) had previously suggested the term gero-dystrophic infantilism for atypical cases.

Gilford (1902, 1904a, 1904b, 1911a, 1911b, 1913) has discussed the subject of progeria at length and it has been reviewed by Apert and Robin (1927), Curtin and Kotzen (1929), Atkinson (1937), Schachter-Nancy (1938), Mitchell and Goltman (1940), Schondel (1943), Gorter (1942), and Wiedemann (1948).

Report of a Case

History. S.R. came under our observation on September 21, 1946, when he was 22 months old on account of failure to gain weight (Figs. 3 and 4). He has been examined at intervals over a period of two and a half years, and the present description (June, 1949) refers to his condition at 4½ years of age.

His mother did not suffer from any illness throughout her pregnancy. Normal delivery took place at term and the birth weight was 5 lb. 4 oz. (2,382 g.). No abnormality was noted at that time. A normal amount of scalp hair was present and the skin appeared to be of normal texture.

He is the first child of the present marriage. His mother, by a previous marriage, has another male child aged 11 years who is normal. There have been no stillbirths or miscarriages. Father, mother, and half-brother are well, and have not suffered from any relevant illnesses. The mother is of average stature, but the father's stature is below average; he has a small head and poorly developed chin but in no other detail does he resemble his son. No history of abnormal physical development in other relatives has been obtained.

FIG. 3—S.R. aged 1¾ years showing typical stance.

S.R. was breast fed for two months and fed thereafter on National Dried Milk and cow's milk. His mother described him as 'a difficult feeder.' One teaspoonful of cod liver oil was given daily when three months old but this was continued for only a few months. He received no additional vitamin C. He was a contented baby and apart from difficulty in feeding and poor appetite he remained well until the age of 18 months, his growth approximating to that of a normal child. He sat up at 7 months, began to talk at the same age and walked at 9 months. His first tooth did not appear until he was over one year old.

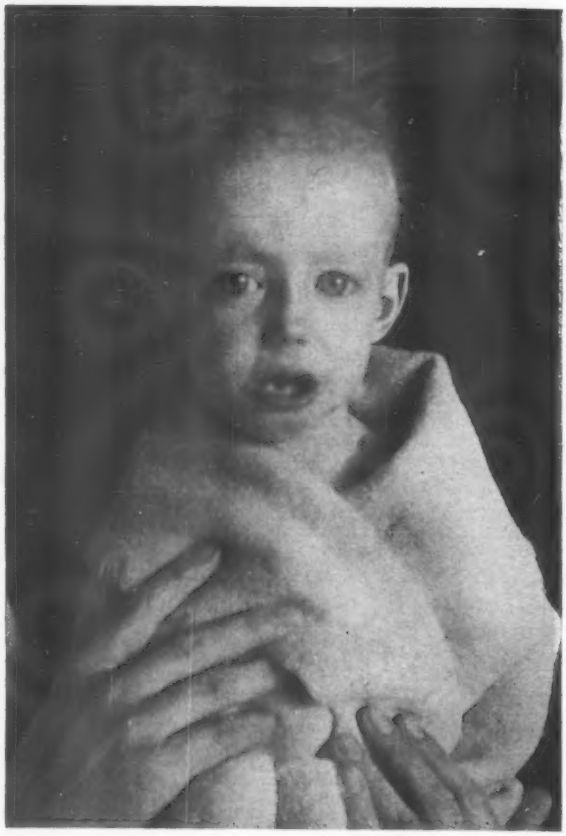

FIG. 4—S.R. aged 1¾ years. Scanty hair and crowded lower teeth.

When he was about 20 months old his parents began to realize that he was only gaining weight very slowly and was looking thinner. His hair was becoming sparse. His appetite remained poor. He has become increasingly bald and prominent scalp veins have been noticed. A change in the facies to a sharp pinched appearance has occurred and he has gradually become thinner. During the last two and a half years his weight has increased by just over 4 lb. as against an expected gain of almost 10 lb.

His mother considers him to be well advanced intellectually for his age. He is fond of playing with companions, likes to be the centre of attraction, and is easily offended. He prefers playing with toys to looking at books, likes to sing and does so in a high pitched voice. He sleeps well but when asleep his eyes remain half open.

TABLE 2

MEASUREMENTS OF PRESENT CASE COMPARED WITH THOSE OF AN AVERAGE BOY

	S.R.	Normal
Weight	19 lb. 14 oz. (9·0 kg.)	37 lb. 5 oz. (16·9 kg.)
Height	35 in. (88·9 cm.)	41·5 in. (105·4 cm.)
Head circumference	18¾ in. (47·6 cm.)	20 in. (50·8 cm.)
Length of clavicle	2⅜ in. (6·03 cm.)	3½ in. (8·9 cm.)
Head—umbilicus	16½ in. (41·9 cm.)	20 in. (50·8 cm.)
Umbilicus—feet	18½ in. (47·0 cm.)	21½ in. (54·6 cm.)
Length of lower limbs	19¼ in. (48·9 cm.)	20 in. (50·8 cm.)
Length of upper limbs	16 in. (40·6 cm.)	18 in. (45·7 cm.)
Chest circumference (at nipple)	17 in. (43·2 cm.)	22 in. (55·9 cm.)
Abdominal circumference (at umbilicus)	18½ in. (47·0 cm.)	19 in. (48·3 cm.)

His limit of walking is half a mile but otherwise he has not been noted to tire unduly easily and dyspnoea has not been marked. He does not sweat much. There is a tendency to constipation. When he becomes excited or on exertion a soft 'rushing' sound is heard in his head by those sitting close to him.

The general appearance of the patient when we examined him in June, 1949, was striking. In his smallness of stature, his restless activity, his impish behaviour and ready recourse to tears, his high-pitched, piping voice and his interest in playthings, he was a small boy; in his thinness and absence of subcutaneous fat, his bald head and pinched facies, his dry, atrophic, inelastic skin, his wrinkled hands, his bent posture and slightly flexed joints, he was an old man.

His demeanour on examination was shy and resentful to begin with but determined, even assertive, when he became accustomed to the examiner. He was easily upset and had a quick temper. If thwarted he showed the irascibility of old age.

His measurements contrasted with those of an average boy of the same age are set out in Table 2.

The head suggested a slight degree of hydrocephalus but this was due to the smallness of the face and not to true hydrocephalus. The circumference of the head was actually less than that expected. The fontanelle was closed (closed on first examination when aged 22 months). Apart from a few almost white downy hairs the head was completely bald giving a 'plucked bird' appearance. The skin over the cranium was thin and tightly drawn and could not be raised easily into folds. Scalp veins were prominent and distended (Fig. 5). The face was small, the skin glazed and atrophic, and the nasal cartilages conspicuous. There was a complete absence of eyebrows and eyelashes and the eyes were prominent. The ears stood out but the lobules were poorly developed. The tympanic membranes were normal. The lips were thin and the mouth small. The lower jaw was small and receding (Fig. 6). There was no limitation of the range of movement of the temporo-mandibular joint. The tongue was smooth. The tonsils were not enlarged and the cervical lymph glands were impalpable. The palate was not unduly arched. Sixteen teeth were present, the posterior molars being absent. Due to the small size of the lower jaw the teeth there were crowded together, the central incisors being rotated and displaced backwards. The submaxillary glands and the thyroid gland were palpable. The temperature was normal.

The thorax was pyriform in shape, the narrowed inlet being associated with very short clavicles. Prominence of the ribs and absence of subcutaneous fat were marked. The nipples were present but small. The chest circumference was less than normal and the chest expansion was ½ in. The respiration rate was 24 per minute. The percussion note over the lungs was resonant and the breath sounds vesicular. There were no adventitious sounds. There was no visible praecordial pulsation, the apex beat being palpable in the fifth left interspace just within the nipple line. On percussion the upper border of cardiac dullness was at the level of the third rib, the right border being at the mid-sternal line. The pulse was regular and the pulse rate was 116 per minute. Sinus arrhythmia was not present. Auscultation revealed a widespread systolic murmur heard over the whole praecordium but most intense over the third left costal cartilage. This murmur was conducted loudly up both carotids to the mastoid processes and then converged to an area of maximum intensity over the occiput where a bruit almost musical in quality and loud enough to be heard on occasions without a stethoscope was present. Pressure over the carotids did not abolish the bruit. The blood pressure was 106/64. He was considered to be suffering from a congenital cardiac lesion although the precise type was not identified. No hardening of the radial or temporal arteries was detected.

The abdomen was full and this in association with the

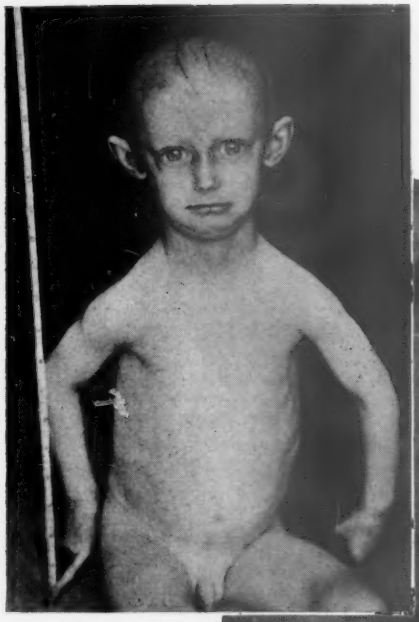

FIG. 5—S.R. aged 4½ years. Very scanty hair, distended scalp veins, full abdomen.

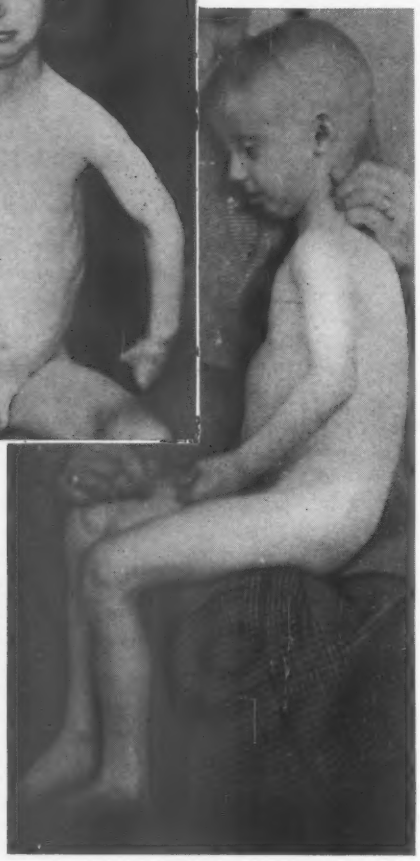

FIG. 6—S.R. aged 4½ years.

narrowed chest gave the child a pot bellied appearance. The fullness appeared to be due to laxity of the abdominal wall. The skin was atrophic and subcutaneous fat absent except in the pubic region where an isolated pad was present. The umbilical depression was obliterated. The liver was not enlarged and the spleen and kidneys were not palpable. There was no abdominal tenderness. The genitalia were of normal development for his age, the scrotum showing the usual rugosity.

Examination of the central nervous system revealed no abnormality of the deep or superficial reflexes. The pupils were equal and reacted to light and accommodation. There was no squint, nystagmus, or abnormality of the optic fundi. Motor power was fair and no abnormalities of sensation were detected.

The limbs were very thin, especially distally, and this thinness accentuated the joint enlargement, particularly of the knees and the knuckles. The hands were small and senile in appearance with wrinkled dorsal skin. There was slight enlargement at the interphalangeal joints and inability to extend these joints fully. The interossei muscles were atrophied. The nails were shortened and their width exceeded their length. The knees and hip joints could not be extended through their full range. There was the typical 'horse riding' stance, the knees and hips a little flexed, the trunk and head held forward with the eyes raised to compensate for this, the arms adducted and slightly flexed at the elbows, the wrists in the mid position between pronation and supination and the fingers flexed (Fig. 7). The gait was straddling but he could run fairly well in rather a flat footed manner.

Special Investigations.—Urine Acid. Specific gravity, 1,010. Albumin, a trace. No sugar. Urobilinogen, a trace. Urinary output in 24 hours, 362 ml. Urea output per 24 hours, 6·9 g. Urinary creatine output per 24 hours, 121·8 mg. Creatinine output per 24 hours, 165·0 mg. Creatine/creatinine ratio, 74% (normal 40%). Creatinine coefficient, 18·5 (normal 15-27·5). Secretion of 17-ketosteroids per 24 hours (as androsterone), 2·85 mg. (normal 0·8-2·6 mg.).

FIG. 7—S.R. aged 4½ years.

BLOOD. Haemoglobin (Sahli), 76%. Red blood cells, 4,000,000 per c.mm. White blood cells 6,400 per c.mm. Erythrocyte sedimentation rate, 22 mm. per hour (micro - method, normal <10). Blood urea 48 mg. %. Blood sugar (fasting), 90 mg. %. Blood cholesterol, 275 mg. %. Total plasma protein, 7·25 g. %. Plasma albumin, 5·00 g. %. Plasma globulin plus fibrinogen, 2·25 g. %. Serum calcium, 11·1 mg. %. Plasma acid phosphatase 3 King Armstrong units %. Plasma alkaline phosphatase 7 King Armstrong units %. Wassermann reaction, negative. (Maternal and paternal Wassermann reactions, negative.)

CEREBROSPINAL FLUID. Fluid clear and under normal pressure. Protein, 10 mg. %. No pleocytosis. Lange reaction, 0000000000. Sugar present. Wassermann reaction, negative.

ELECTROCARDIOGRAPHIC. Tracing showed regular rhythm of sinus origin. No sinus arrhythmia present. Heart rate, 108 per minute. PR interval, 0·10 secs. QRS complex M shaped in lead III.

RADIOLOGICAL. The cranial wall was thin. There was no premature synostosis. The pituitary fossa was enlarged beyond normal limits (Fig. 8). There was no anodontia, the unerupted molars being seen. The degree of calcification of the permanent dentition corresponded with his age.

The lung fields were clear. The heart was not enlarged and showed normal configuration. The clavicles were short and thin and the ribs narrow (Fig. 9).

Spina bifida of the first sacral segment was seen on stereoscopic examination, and on lateral view the vertebrae were of the ovoid infantile type.

Marked bilateral coxa valga was present (Fig. 10).

FIG. 8.

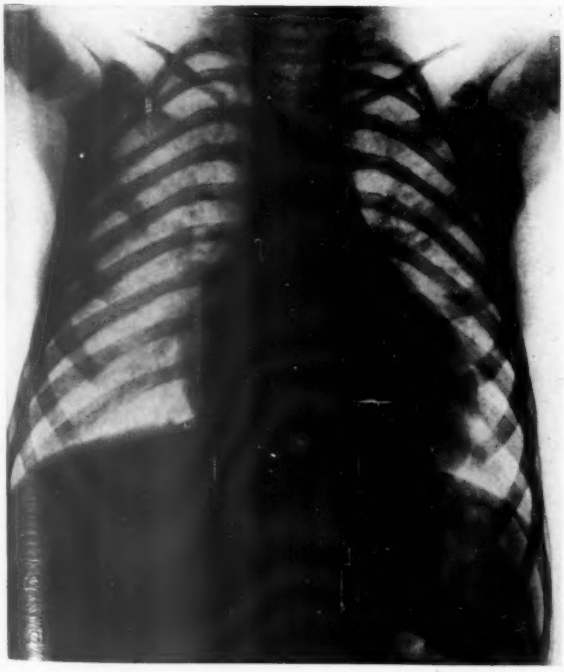

FIG. 9.

Figs. 8, 9 and 10. Radiological appearance of skull, chest and pelvis.

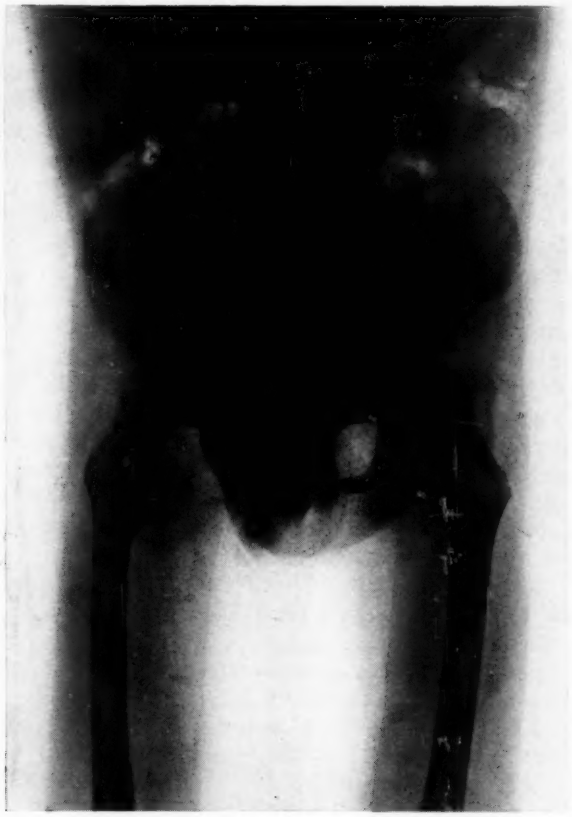

FIG. 10.

At the age of 3½ years the ischial and pubic rami had almost fused as compared with a normal age of fusion of 4 to 5 years.

The shafts of the long bones were slender, the ends being of normal width. At the age of 22 months the state of ossification of the ankle and foot was slightly in advance of that expected. At the age of 4½ years the carpus showed an ossification age of 3 to 3½ years (Fig. 11).

An intravenous pyelogram showed normal excretion of dye and no abnormality of the kidney pelves, ureters, or bladder.

Discussion

Clinical Features. The case here described exemplifies most of the classical clinical features of

progeria as seen at this age. Cases have been distributed widely throughout the world and a case in a negro has been described (Schwartz and Cooke, 1945). In a few cases there has been a history of maternal illness during pregnancy (Gilford, 1897; Curtin and Kotzen, 1929; Popek and Hadlik, 1938), no specific illness appearing to be significant.

The average birth weight in ten cases where this was stated was 5 lb. 13 oz. (2·65 kg.) and apart from prematurity in some instances (Variot and Pironneau, 1910; Curtin and Kotzen; Broc, Nicolle, and de Beaujeau, 1935) no abnormality was noted at birth, failure to gain in weight and loss of hair in the second year of life being the usual reasons causing parents to seek medical advice. There is no apparent hereditary or familial factor nor relationship with the parity of the mother. The sex incidence is equal. The initial failure to gain in weight and stature develops gradually into one of dwarfism. Fig. 12 compares graphically the growth in weight curves in progeria and in normal individuals. Fig. 13 compares the corresponding growth in height curves. It will be noted that up to the second year there is only slight retardation of growth but that thereafter it is very slow, 36 lb. (16·5 kg.) being estimated as the average weight reached at the age of 18 years and 46 in. (117 cm.) the average height at the same age. The average age at death in seven cases was 16¼ years, the oldest recorded case surviving until the age of 26 years (Manschot, 1940).

Walking and speaking have occurred early in some cases but in a few have been delayed. The primary dentition is delayed. Appetite may be very good or poor. An undue sensitivity to heat and cold has been noted in certain cases (Gilford, 1897; Mitchell and Goltman, 1940). Sleeping with the eyes half open has also been reported by Zeder (1940).

All cases show a striking resemblance in physical features and in body configuration. The facial features are quite unlike those of other members of their families, but compared with other cases of progeria at similar ages are remarkably alike, so much so that Gilford writing of his two cases tells how the father of one of them, when shown a photograph of the other, thought at first that he was looking at a portrait of his own son. Due to the smallness of the face all have a hydrocephalic look and the relative reduction in the size of the orbital cavities is probably responsible for the prominence of the eyes. A case in which there was microphthalmia has been reported by Schondel (1943). Prominent dilated scalp veins are invariably present. Frequently the palate has been high and arched and the fontanelle late in closing. Micrognathia involving the lower jaw always occurs, with crowding and irregularity of the teeth, especially the incisors.

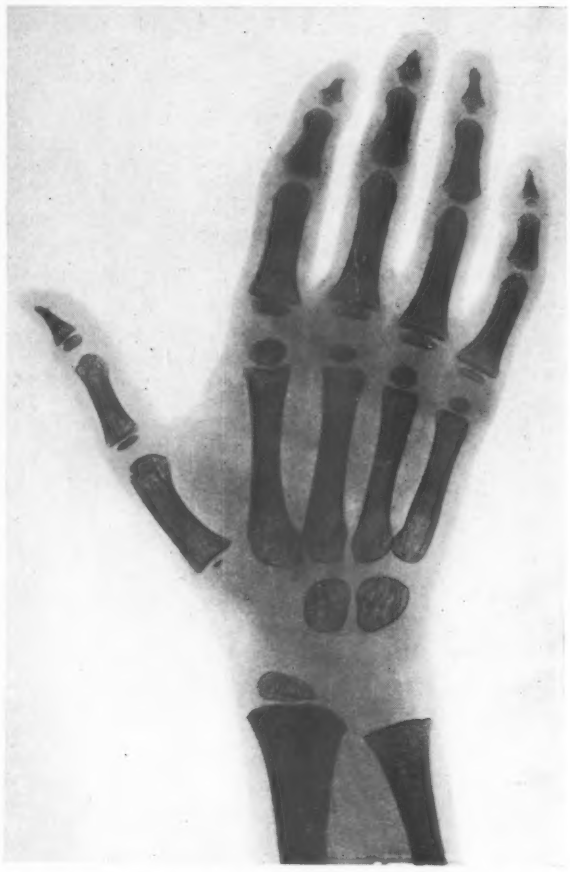

FIG. 11.—Radiograph showing ossification age of the carpus of 3 to 3½ years.

Some of the teeth may be absent. Baldness and absence of the eyebrows and eyelashes, the atrophic, inelastic state of the skin, and the absence of subcutaneous fat except in the pubic region are marked in all cases. In some, small pigmented or unpigmented spots on the skin have been noted, and in some, the nails have been furrowed and membranous. In three cases (Strunz, 1926; Exchaquet, 1935a and b, and Zeder, 1940) the condition has been associated with sclerodermia.

The clavicles are characteristically short and the thorax pyriform in shape, contrasting with the prominent abdomen below. The ribs are usually prominent. The umbilical depression is obliterated. The heart is not enlarged but cardiac murmurs are frequently present. Cranial bruits have been noted previously by Talbot, Butler, Pratt, MacLachlan, and Tannheimer (1945). The possible vascular abnormalities associated with such bruits have been discussed by Hamburger (1931). The blood pressure is normal. Schwartz and Cooke (1945) have recorded

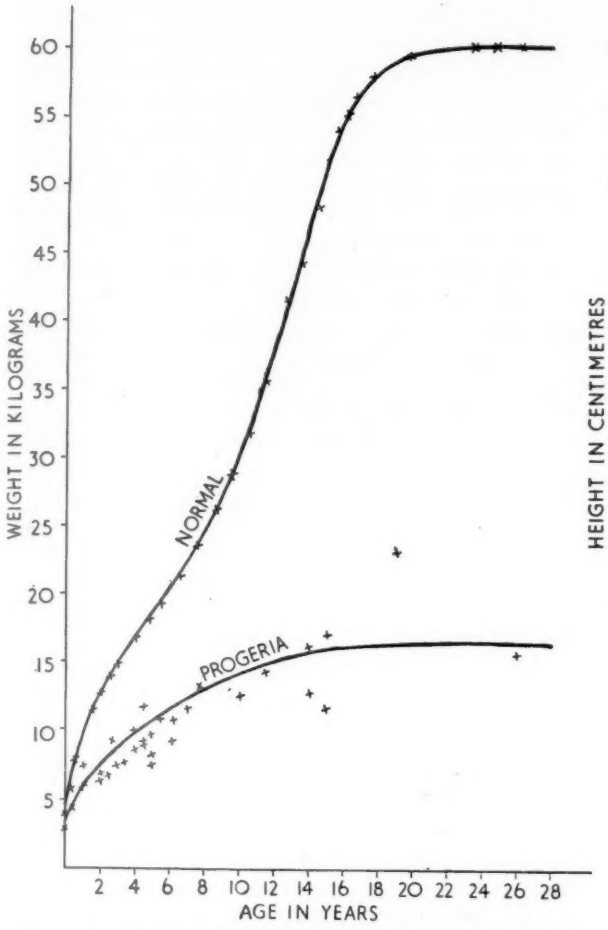

FIG. 12.—Growth in weight curves in the normal (after Mitchell-Nelson) and in Progeria.

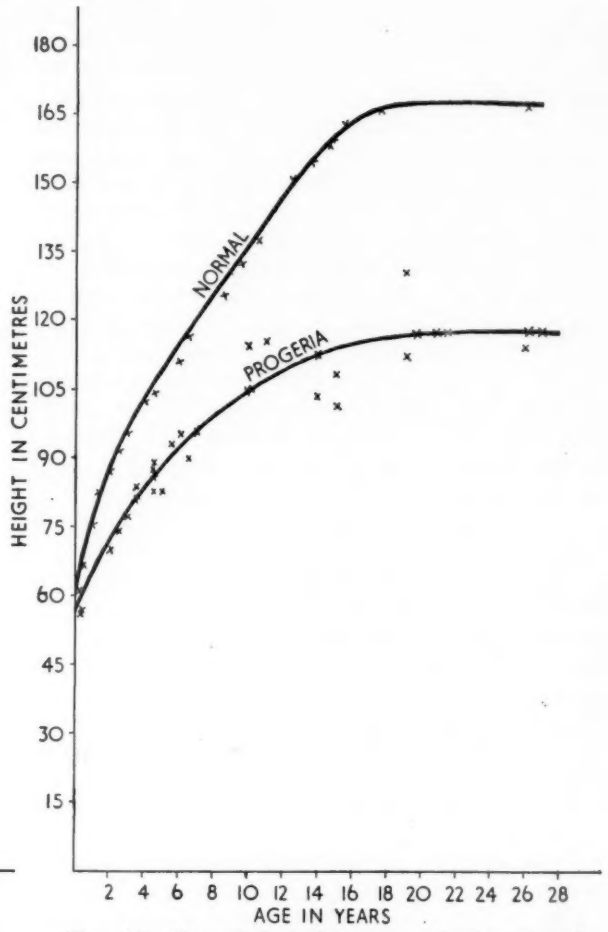

FIG. 13—Growth in height curves in the normal (after Mitchell-Nelson) and in Progeria.

arteriosclerotic changes as early as the fifth year and these are a well marked feature of all older cases. The genitalia are normal until the age of puberty but in the few reported cases beyond the age of adolescence there has been little evidence of sexual maturity. Spermatogenesis has been reported in one case (Gilford, 1897), but in other cases (Orrico and Strada, 1927; Talbot *et al.*, 1945) no evidence of this was found on post-mortem examination.

No characteristic central nervous system abnormalities have been noted.

The muscles are poorly developed and the limbs are thin. There is some enlargement of the joints and usually limitation of movement, especially of extension. The knees, the interphalangeal joints and the shoulders are frequently so affected. Arthritis has occurred as early as 6 years of age (Schiff, 1934; Schwartz and Cooke, 1945), and has been a prominent feature in the older cases. Zeder describes the hand as like a 'dead hand' and the posture as 'horse riding.'

The intellect in most cases is normal or above normal. In the earlier years a slightly precocious mentality, as in the case here reported, is characteristic. Later, increasing desire for withdrawal from company, reserve, and attacks of depression tend to occur.

Anginal attacks have occurred as early as the age of 7 years (Talbot *et al.*, 1945) and are reported in most of the older cases. They have usually been of serious significance. Dyspnoea has been marked in some cases but not in others. Hemiplegia at the age of 7 years (Curtin and Kotzen, 1929) and 19 years (Orrico, 1918) has been reported. Where death has occurred preceding clinical evidence of progressive arteriosclerotic and atheromatous changes involving especially the coronary arteries has usually been present, coronary occlusion being the most frequent terminal event.

Radiologically, thinning and some decalcification of the shafts of the bones, a poorly developed mandible with crowding and abnormal development of the teeth, short clavicles and coxa valga are the most characteristic findings. Enlargement of the sella turcica has been reported previously (Exchaquet, 1935b, Zeder, 1940). The vertebrae tend to retain the ovoid notched infantile shape longer than usual (Brailsford, 1948). Delayed closure of the fontanelle and defective ossification of the bones in the posterior part of the cranium (Thiers and Nahan, 1933; Broc *et al.*, 1935) and arthritic changes in the joints have also been reported. Thiers and Nahan considered their case to have had associated cleidocranial dysostosis. Shortening of the clavicle, however, is a constant feature of all cases of progeria and there is no familial element.

A raised creatine/creatinine ratio does not appear to have been recorded previously.

The cytology and chemistry of the blood do not show any characteristic changes. The high serum calcium figures noted by Exchaquet (1935b) and Zeder are unusual. Like the case here reported a raised E.S.R. was noted by Zeder and a raised blood cholesterol level by Exchaquet (1935b). Apart from one case (Orrico, 1918) the Wassermann reaction of the blood has been negative.

Varied electrocardiographic changes have occurred.

Diagnosis. As already stated we reserve the term progeria for cases exhibiting the classical features shown in Hutchinson's and Gilford's original reports. Such cases are readily recognized after the age of two years. Some of the cases reported as progeria appear to be examples of the Werner syndrome (Thannhauser, 1945), others of ectodermal dysplasia (Harris, 1927). By its absence of hair alopecia totalis in children may present a superficial resemblance to progeria.

Pathology. We are today little nearer an understanding of the pathological processes associated with progeria than Gilford was half a century ago. We can watch the occurrence, over a span of 10 or 15 years, of changes of senility which would normally take five or six times as long to develop. Were we to understand the pathology considerable light might be shed on the processes of ageing. The changes are not, however, merely those of senility. They are those of senility imposed at an infantile stage of development so that infantile characteristics persist side by side with senile ones. This is seen particularly in the bony skeleton, and Keith (1913) has pointed out as infantile characteristics, its small size, the development of the forehead, face, and jaws, the frequent delay in closure of the fontanelle, the thin cranial walls, the persistence of certain cranial sutures, the delay in ossification of certain centres and the shape of some of the bones; and as senile characteristics, the decalcification, the premature fusion of certain sutures, the advanced ossification in certain centres and the arthritic changes. Examples of senile change other than in the skeleton are seen in the presence of atrophic skin and arteriosclerosis.

Few studies of progeria in life have been made, but the metabolic investigations of Talbot *et al.* on one case are interesting. They concluded (1) that the dietary caloric intake was adequate and that the failure to gain weight was due to an excessive total energy output; (2) that this excessive energy output was not due to hyperthyroidism; (3) that testosterone would increase protein anabolism relative to protein katabolism as shown by an increase in musculature but that this change took place at the expense of other tissues as there was little gain in total weight; (4) that a therapeutic reduction of the total energy output by thiouracil caused a gain in total weight but the possibility that this was due to myxoedema could not be excluded. Other observers have noted a raised basal metabolic rate but the altered skin surface area in progeria may have given false results. The basal metabolic rate has also been reported to be reduced (Popek and Hadlik, 1938).

Raised serum calcium levels were noted by Exchaquet and Zeder and poor calcification of bones is a frequent radiological finding. Both cases showing raised serum calcium were associated with sclerodermia, a condition in which the serum calcium level may be raised (Cornbleet and Struck, 1937).

Post-mortem studies have been reported in four cases (Gilford, 1897; Orrico and Strada, 1927; Manschot, 1940; Talbot *et al.*, 1945). These showed the following constant features: very scant subcutaneous fat although fat was not entirely absent, slender shafts of the long bones with relative width at the epiphyses, marked generalized arteriosclerosis especially in the kidneys and atheroma and calcification of the aorta and coronary arteries with coronary narrowing. In Gilford's case the thymus was enlarged and there was coronary occlusion. The pituitary was not particularly examined. In Orrico's case (Orrico and Strada, 1927) there was well marked hypoplasia and sclerosis of the adrenal cortex. The thyroid was small and only three small parathyroids were found. The testicles were small and there was a complete absence of spermatogenesis. The prostate was small. The pituitary weighed 0·35 g. (normal 0·49 g.) and a large cyst was present in the region of the pars intermedia. The eosinophil cells were normal in

number but were larger than usual and had finely granular protoplasm. In the case of Talbot *et al.*, the thymus was enlarged, the parathyroids could not be found and the pituitary was asymmetrical and weighed 0·61 g. (normal 0·29 g.). It was not examined microscopically. There was no histological evidence of spermatogenesis. Coronary thrombosis and a myocardial infarction were present. The lateral cranial venous sinuses showed an abnormal course, an interesting finding in view of the cranial bruit present in life. In Manschot's case the heart was enlarged, there was hyaline degeneration and fibrosis of the thyroid, and the parathyroids, three in number, were small and infantile. The pituitary weighed 0·4 g. (normal 0·49 g.), and histologically a deficiency of the eosinophil cells of the anterior lobe was noted. The adrenals were large but the zona granulosa of the adrenal cortex was poorly developed and contained much fat.

The pituitary abnormalities and parathyroid deficiency in the last three cases are interesting, the latter in view of the invariable generalized osteoporosis and occasional high blood calcium level which occur.

The unpublished post-mortem examination by Ebbs (1949) on Parsons' (1949) case showed wasting, premature ageing, coronary occlusion, and coronary artery sclerosis.

Several theories have been advanced to explain the condition. Gilford was impressed by the contrasting features of progeria and acromegaly. His original name for the syndrome he described was in fact micromegaly. In the light of more recent knowledge this contrast between acromegaly and progeria becomes more marked. On the one hand the gigantism, the hirsutism, the thick lips, large tongue, heavy lower jaw, large clavicles, thickened skin, gruff voice and large hands in acromegaly contrast on the other hand with dwarfism, paucity of hair, thin lips, small tongue, underdeveloped lower jaw, short thin clavicles, atrophic skin, piping voice and small hands of progeria. In other words we have in the one case a selective hyperplasia of certain parts and in the other a selective hypoplasia of the same parts. In the late stages of acromegaly when pituitary insufficiency supervenes the skin becomes atrophic and thin, the hair falls out and arteriosclerotic changes may develop. Some contrasting features between cases with tumours of the adrenal cortex and cases of progeria might also be mentioned; the hirsutism, the precocious genital development and the obesity of the former and the absence of hair, the retarded genital development and the thinness of the latter. Variot and Pironneau (1910) considered that the condition was probably of uprarenal origin and Nasso (1925) that it was a polyglandular disturbance with an absolute incapacity of the tissues to develop. Orrico agreed with this view of the polyglandular nature of the condition. Strunz (1929) considered that hypofunction of the anterior lobe of the pituitary was the underlying disturbance and Exchaquet suggested that in his case there might be hypofunction of the acidophil cells of the anterior lobe of the pituitary associated with a basophil adenoma. Zeder considered that the condition was probably a form of pituitary dwarfism and that the parathyroids were particularly influenced by the pituitary dysfunction. He also suggested that the hypothalamus might be involved. Greene and Paterson (1943), in discussing a case of sudden senescence in an adult following a fall, suggested hypothalamic disturbance as the possible cause. Wiedemann (1948) has pointed out the extent to which mesodermal derived tissues are involved in progeria and has elaborated the conception of a constitutional mesenchymal dysplasia.

While the contrast with acromegaly is striking there is some similarity with Simmonds' disease. In both there is the appearance of early senility and loss of hair and subcutaneous fat, both may show asthenia and failure of sex function, in both there may be some glandular atrophy especially of the thyroid and adrenals although this latter is not so constant in progeria as it is in Simmonds' disease. Nor does progeria show the gross asthenia of Simmonds' disease and the myxoedematous changes which may be associated with the latter condition do not occur. Hypoglycaemia and hypoglycaemic attacks are not a feature of progeria nor is hypotension.

We believe from the evidence available that the primary defect in progeria is one of pituitary dysfunction. The marked contrast to acromegaly and points of similarity to Simmonds' disease, both conditions accepted as of pituitary origin, would support this belief. Abnormalities of the sella turcica have been noted radiologically and of the pituitary at post-mortem examination. Radiologically, Exchaquet noted absence of the anterior clinoid processes and deficiency of the posterior clinoids. The fossa was enlarged in Zeder's case and in ours. Keith on the other hand noted that the sella turcica was smaller than normal in the progerian skull he described. Macroscopically the pituitary in Orrico's case showed a cystic abnormality and in the case of Talbot *et al.*, was asymmetrical. Manschot's histological studies showed a deficiency of the eosinophil cells of the anterior lobe, Orrico and Strada's alterations in their size and protoplasm. As hyperfunction of the eosinophil cells of the pituitary may produce the changes of acromegaly it seems logical to deduce that

hypo-function of these cells at an early age may produce the characteristic changes of progeria.

Treatment. Little can be said about this. No treatment has proved effective. Thyroid, pituitary growth extracts, testosterone, thiouracil, short wave diathermy and ultra violet radiation have been tried without any appreciable benefit. Should the condition prove to be a pituitary hormone deficiency it would seem reasonable to suppose that increased knowledge of the pituitary hormones and the ability to isolate them individually in therapeutically active forms might lead to adequate replacement therapy.

Summary

A classical case of progeria is described. The world literature relating to this subject is reviewed and it is concluded that this is the nineteenth typical case to be reported. Approximately as many atypical cases have been described and a separate grouping and naming of these is advocated. The clinical features, diagnosis, pathology, and treatment of progeria are discussed. It is suggested that dysfunction of the anterior lobe of the pituitary, possibly of the eosinophil cells, is the underlying lesion.

It is a pleasure to acknowledge our indebtedness to Dr. J. H. Prain who has carried out the biochemical estimations, to Drs. G. M. Grant, T. Sprunt and W. C. Swanson for the radiological examinations, and to Drs. M. G. Green, D. Grewar and Mr. Allan for the photographs. Figs. 1 and 2 are reproduced by kind permission of the Editors of the *Proceedings of the Royal Society of Medicine*. The British Council has given valuable help in obtaining some of the rarer references.

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A CASE OF SPORADIC CONGENITAL GOITRE

BY

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Since the general use of iodine prophylactically in endemic goitre areas gross enlargement of the thyroid gland at birth has become relatively uncommon. Wegelin's (1926) series in the pre-iodine period of 223 consecutive necropsies on newborn infants in a goitre area between 1911 and 1921 showed that 34% had thyroid glands weighing over 6 g. The normal weight of the gland at birth in a healthy infant is 1·5 to 2 g.

The following case is apparently one of sporadic congenital goitre without any evidence of thyroid dysfunction or goitre in the mother or her family. Surgical intervention afforded an interesting opportunity to examine histologically the thyroid gland at two different stages after treatment with thyroid extract.

Case Report

R.B., a boy and the first child, was born on September 10, 1948. His birth weight was 7 lb. 7 oz.

The mother's history revealed no evidence of goitre, hypothyroidism, or dietary deficiency, and no possible goitrogenic drug had been taken. She had never lived in an area regarded as goitrous and the family history was free of thyroid disease.

The baby was born at term but delivery by forceps was necessary on account of a prolonged second stage labour, possibly due to poor foetal head flexion. At birth the neck was noted to be grossly swollen causing extreme head retraction, and stridor developed a few days later together with difficulty and cyanosis during feeds. The infant was admitted to Worcester Royal Infirmary when 10 days old and transferred the following day to the Birmingham Children's Hospital.

The appearance of the infant was arresting (Fig. 1). The face was congested and the head hyper-extended because of a large, soft, bi-lobed swelling with a well developed isthmus high up in the neck which obscured all the normal anatomical structures. The swelling had the configuration of a grossly enlarged thyroid gland, but the consistency of a cystic hygroma; it was quite symmetrical, was not transilluminable, and moved on deglutition. No bruit was audible.

A lateral radiograph of the neck demonstrated a large soft-tissue mass in the neck which was displacing the pharynx, larynx, and upper part of the oesophagus forwards and causing considerable angulation (Fig. 2).

The blood cholesterol level was 160 mg. %.

Treatment. Treatment with thyroid extract and iodine was started at once; thyroid (gr. ¼) and Lugol's iodine (minims 2) were given daily from the thirteenth to the twenty-seventh day of life. No improvement of the dyspnoea or stridor followed and surgical relief became imperative.

The first operation was performed on October 9, 1948, (A.L. d'A.). Owing to distortion of the larynx and trachea a tracheal tube could not be passed. Through a collar incision the left lobe of the thyroid gland was

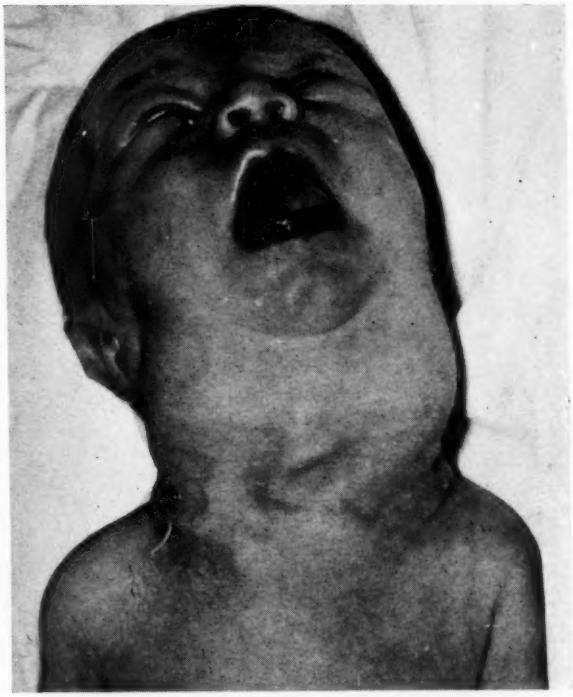

FIG. 1.—Condition on admission.

FIG. 2.—Lateral radiograph of the neck on admission.

exposed and found to be very large with a retrolaryngeal portion and a retrosternal prolongation. Five-sixths of this lobe was resected. The parenchyma of the gland was not very vascular but the superior and inferior thyroid arteries were large and were ligated away from the gland. Only one lobe was dealt with because:

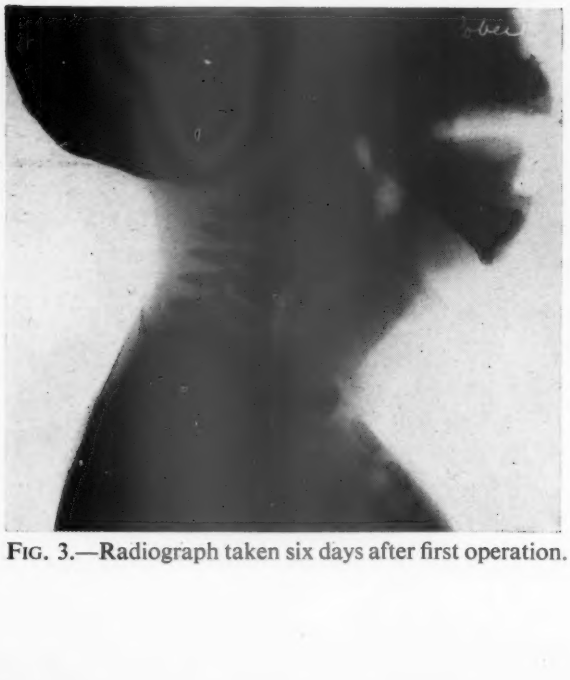

FIG. 3.—Radiograph taken six days after first operation.

(1) The retrolaryngeal and retrosternal portions were considered to be the cause of the respiratory obstruction and their removal would overcome the associated pressure symptoms. (2) Hemithyroidectomy as an emergency operation was considered to be as much as could safely be undertaken in an infant of this age. (3) If relief was inadequate further thyroid tissue could be removed later.

The respiratory obstruction was immediately relieved, but within a few days the stridor and the feeding difficulty returned, though to a less extent than previously. The radiograph (Fig. 3) taken at that time shows less angulation and less forward displacement of the larynx and trachea. Accordingly thyroid extract, this time in the larger dose of gr. ½ daily, was administered from the tenth post-operative day, and was increased on the twenty-first post-operative day to ¾ gr. per day. During the next fortnight the neck swelling decreased in size, but the baby began to show signs of mild hyperthyroidism with restlessness, tachycardia, and a voracious appetite, and was taking nearly 70 calories per pound per day of a milk mixture. The thyroid extract dosage

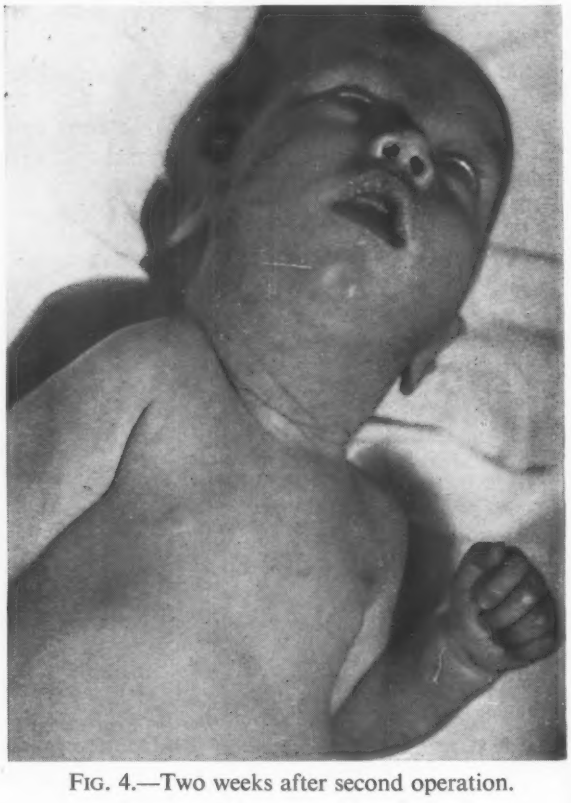

FIG. 4.—Two weeks after second operation.

was therefore reduced to ½ gr. daily seven weeks after operation. The blood cholesterol level at this time was 130 mg. %. A week later the infant, now three months old and weighing 10 lb., was still having difficulty with feeding which caused attacks of cyanosis and stridor.

FIG. 5.—Radiograph taken five days after second operation.

The head retraction was as marked as ever. A stage of uneasy equilibrium had now been reached when it was considered that any added burden such as a respiratory infection would probably have proved fatal. For this reason it was considered necessary to undertake further surgical treatment.

The second operation was performed on December 2, 1948 (A.L. d'A.). The right lobe was exposed and found to be much firmer than that previously removed. Retro-laryngeal and retrosternal portions were again present and were removed together with five-sixths of the remaining lobe. The gland was remarkably avascular although the inferior thyroid artery was very large. The post-operative course was uneventful and subsequent progress satisfactory. No further thyroid extract was given. The blood cholesterol level dropped to 114 mg. %. Fig. 4 shows the appearance of the baby 14 days after the second operation, and Fig. 5 is the lateral radiograph taken at the same time. All neck swelling has disappeared and the position of the pharynx, larynx, and trachea is now normal. When the infant was last seen at the age of 11 months he weighed 19 lb. 10 oz. and there were no evidences of hypothyroidism except that on exertion a little stridor could be elicited (Fig. 6).

Pathological Reports

The first specimen was obtained after thyroid extract gr. $\frac{1}{4}$ and Lugol's iodine minims 2 had been given for 14 days, and the second after 44 days of treatment with thyroid $\frac{1}{2}$ or $\frac{3}{4}$ gr. a day to the limit of tolerance. Dr. Baar reported on the specimens as follows:

The first specimen removed on October 9, 1948, consisting of the left lobe of the thyroid gland and part of isthmus, measured 4 × 3 × 2·5 cm., and was well encapsulated. The cut surface was smooth and yellowish grey in colour with narrow strands of white tissue. The vesicles are lined by columnar, or occasionally cubical, epithelium with a cell height of 17·5 to 25μ. One or two papilliform proliferations of the epithelium can be seen. The lumina are very small and mostly empty of colloid which when present takes stain poorly. The stroma is scanty and not hyperaemic, the strands being 12·5 to 150μ (Fig. 7).

The second specimen, removed on December 2, 1948, consisting of the right lobe of the thyroid, measured 4·5 × 3 × 2·2 c. and weighed 14·8 g. No vesicular structure was seen macroscopically.

Vesicles are larger than in the previous specimen, the diameter being 15 to 50μ, and the cell height is 6·25 to 7·25μ. More of the vesicles contain colloid which is still pale and often granular. The stroma is more abundant and the strands vary from 25 to 500μ in width. The histological picture is that of hyperplastic thyroid tissue with evidence of incipient involution (Fig. 8).

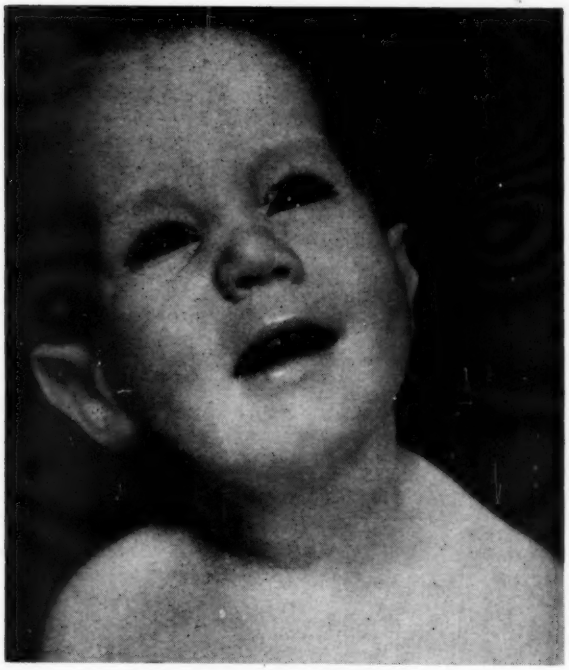

FIG. 6.—Child aged one year.

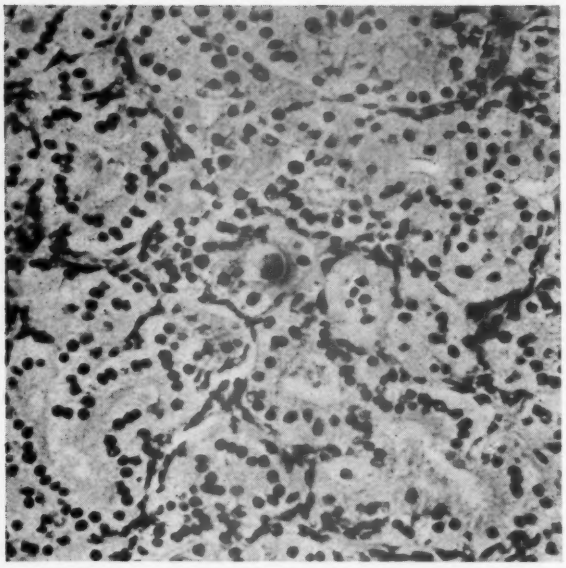

FIG. 7.—Section of thyroid gland removed after 14 days' treatment.

Discussion

The cause of the enlargement of the thyroid in this infant is difficult to explain. It has been shown by Skinner (1924 and 1928) that a deficient iodine intake by a woman during pregnancy is an important factor in the production of thyroid enlargement in infants at birth, but there is no evidence to suggest any such deficiency in our case. Hypothyroidism or maternal goitre are other causes that have been advanced (Neurath, 1925; Hill, 1933; Davies, 1943); and Solis-Cohen, and Steinbach (1939) postulate that iodine deficiency may cause simple goitre in one generation, hypothyroidism in the second, and congenital goitre or cretinism in the third generation.

Maternal Graves' disease causing enlargement of the thyroid in the newborn infant must be an uncommon occurrence in view of the rarity of pregnancy going to term in such cases. Recently, however, an infant with a moderately enlarged goitre at birth was admitted to the Birmingham Children's Hospital and the mother was found to have definite signs of hyperthyroidism with enlargement of the gland.

The cases reported by Parmelee, Allen, Stein, and Buxbaum (1940), Rienhoff (1940), and Kunstadter (1948) are apparently similar to ours in that they were sporadic and of unexplained aetiology.

In our case there was nothing to suggest thyroid disturbance of the mother either in her history or when seen after delivery, but it is possible that there might have been a latent or temporary hypothyroidism during pregnancy owing to increased demands during this time. Many substances such as cabbage, cyanide, sulphaguanadine and, of course thiouracil, are known to cause temporary thyroic insufficiency. Although this infant's mother admitted to taking aspirin and also received a short course of sulphonamide therapy during pregnancy the necessity for these drugs is too frequent an occurrence in this country to be considered seriously. In this connexion, however, Astwood's (1949) recent work with radioactive iodine for detecting anti-thyroid substances may have considerable significance.

Although Bartels (1941) believes that congenital goitre and endemic cretinism are not inherited, the importance of heredity in some forms of thyroid disease has been emphasized by Jackson (1949), especially in goitre-free areas.

The clinical features in our case were very similar to those described by Wieland (1927) who makes a particular note of the neck extension, the stridor

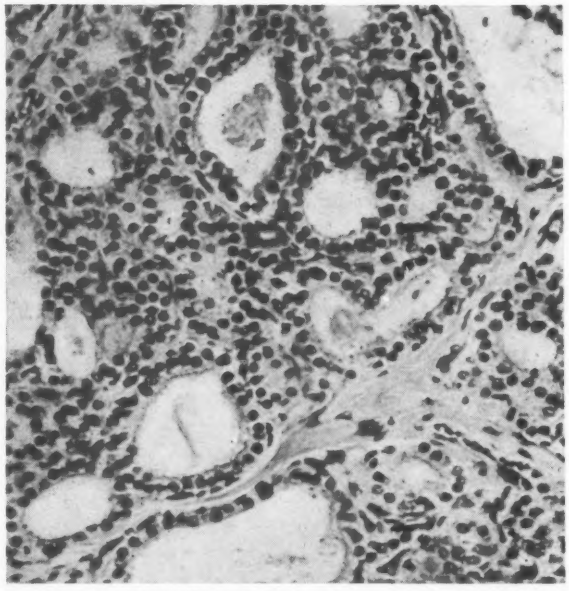

FIG. 8.—Section of thyroid gland removed after 44 days' treatment.

which largely disappears during sleep or on relaxation, the low hoarse cry, and the accentuation of all these symptoms by feeding. Although he states that the prognosis is good if the infants survive after 24 to 36 hours, the literature already quoted concerning the larger glands provides a gloomier picture.

In view of the experience of Plummer and Boothby (1924), Rienhoff (1940), and Smallpeice (1949) we first tried medical treatment with both iodine and

thyroid extract, and from the histological pictures at the different stages of medication with thyroid extract it is apparent that there was a significant regression in the activity of the gland, which tends to confirm the clinical impression of a reduction in size of the neck swelling.

On reflection larger doses (gr. $\frac{1}{2}$ to $\frac{3}{4}$ a day) of thyroid extract from the beginning of treatment might have been more beneficial, but it is most improbable that removal of part of the gland could have been avoided in this particular case.

As regards surgical treatment, tracheotomy is apparently dangerous owing to the risk of subsequent bronchopneumonia at this age. Isthmectomy has been advised but would have been unsuccessful in this case because of the retrolaryngeal and retrosternal portions. The general opinion is that hemithyroidectomy is the operation of choice if surgery becomes necessary. Cretinism may develop even without surgical interference (Hurxthal and Musulin, 1946) and this child will have to be watched carefully, but so far he has not shown any clinical evidence of thyroid insufficiency.

Summary

A case of sporadic congenital goitre causing severe respiratory embarrassment is described.

Despite intensive treatment with both thyroid extract and iodine surgical relief became necessary.

The histological findings in the thyroid gland at different stages of oral thyroid administration are described.

The literature is briefly reviewed and the management of such cases is discussed.

We wish to thank Professor J. M. Smellie for permission to report this case. We are also indebted to Dr. A. G. V. Aldridge, who referred the infant to us, to Dr. Baar for the histological reports, and to Mr. G. Williamson for the photographs.

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CHYLOTHORAX IN THE NEWBORN

BY

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Chylothorax in infancy is an extremely rare condition and a search of the literature has only revealed 13 cases under the age of one year, of which five occurred in the first four weeks of life (Table 1). Only two of these infants survived, and therefore the publication of a further case of a child four days old who recovered spontaneously after two aspirations, seems justified.

Case Report

J.K., a doctor's first child, after an uncomplicated pregnancy, was born at term on June 19, 1948, by forceps delivery for delay in the second stage of labour. The child was asphyxiated at first and responded slowly to routine treatment, but he was crying well 20 minutes after birth. He weighed 7 lb. 6 oz. and externally appeared quite normal, apart from a small right-sided hydrocoele and a small vascular naevus on the back.

After 48 hours he was put to the breast, and, although he seemed to suck well, it was noticed that during feeding he became slightly cyanosed with rapid respirations. Examination of the chest at this time showed no grossly abnormal signs. During the next two days, however, the cyanotic attacks became more frequent and occurred after crying as well as after feeding. Examination of the chest now showed dullness of the right chest with diminished air entry, and a radiograph revealed a right-sided pleural effusion.

Needling was performed on the morning of the fifth day and 45 ml. of slightly opalescent, yellowish coloured fluid was aspirated and replaced with 100,000 units of pure penicillin. The fluid was found to contain 4% protein, but no fat. There were many cells, mainly lymphocytes. No organisms were seen in the direct film and the culture remained sterile.

Following the aspiration, the child was immediately more comfortable and cyanotic attacks were less frequent. On the seventh day a second radiograph still showed a fair amount of fluid, but further needling was not very successful and only a few millilitres of fluid were obtained. It was, however, noticed that the fluid was becoming more opaque.

By the tenth day the cyanotic attacks had become more frequent again. A further aspiration, taking off as much as possible, produced 90 ml. of odourless, milky fluid, only very slightly yellowish in colour. This fluid when analysed now gave the typical findings of chyle; protein 4 g. per 100 ml., cholesterol 48 mg. per 100 ml., fat 0·9 g. per 100 ml.; cells, a few lymphocytes only. The fat was present in very fine emulsion, and there was no apparent alteration in the appearance of the fluid on standing or after filtration through a Whatman's filter No. 42, but a clear yellow fluid was obtained from Berkefeld filtration.

One week later the child seemed much better and there had not been any further attacks of cyanosis. X-ray examination showed no further collection of fluid. At the age of 24 days he was discharged home, fully breast-fed and gaining weight, and his last radiograph was perfectly clear. Shortly after this he was taken to Canada, and at the age of six months he was perfectly fit, weighed 18 lb. and had a clear chest radiograph.

Table 1

Table of Reported Cases of Chylothorax in Neonates

Case	Age (days at onset)	Outcome
Stewart and Linner (1926)	4	Died after repeated daily aspirations for 16 days.
Hilgenberg (1929) ..	5	Diagnosed at necropsy.
Janet, Boegner, and Laquerrière (1936)	21	Recovered after one aspiration.
Everhart and Jacobs (1939)	15	Died after repeated aspirations for three weeks.
Wessel (1944) ..	14	Recovered after 13 daily aspirations.
Present case ..	4	Recovered after two aspirations.

Discussion

That this was a case of chylothorax was subsequently quite obvious, but the diagnosis was not immediately made at the first aspiration because the fluid did not look like chyle and was orange-yellow in colour. It appears, however, that this coloration has been noticed previously in neonatal cases. Stewart and Linner (1926) thought that it was due to pigment (lactochrome) present in the colostrum, but this is unlikely, for the amount of coloration is too great to be accounted for by the small amount of pigment in colostrum, and attempts to colour

chylous pleural effusions by administering dyes by mouth have not been successful. The subsequent change in colour and appearance of the fluid to resemble milk is due to the increase in the amount of fat which is present in a fine emulsified globular state. In the first specimen of fluid obtained in this case, no fat globules could be seen at all and it was reported that the fluid resembled lymph. Apparently it was not till after the child had been on the breast for a few days that fat was being absorbed and passed via the thoracic duct into the pleural cavity. It can easily be shown in cases where the chylous effusion tends to recur after aspiration that the fat content of the chyle varies with the fat content of the diet.

The aetiology of these cases is still obscure. In early infancy they are usually designated as 'spontaneous' which really means that they are of unknown origin. After this age practically all cases of chylothorax are associated with injury. The injury is usually serious, but occasionally, especially in children, it may be only slight. Thus Kirchner (quoted by Janet, Boegner, and Laquerrière 1936) reports the case of a child of nine years who was pushed by another child against a window bar and 15 days later developed a chylothorax. Muttermilch (1902) writes of a five-months-old infant who was dropped out of bed by its mother and in falling knocked against its cradle. It was apparently normal for two to three weeks and was then found to have a chylothorax. In the case of Everhart and Jacobs (1939), delivery was complicated by cyanosis of the child due to the cord being tightly round the neck and it required vigorous attempts by the accoucheur to revive the child. In the other neonatal cases all the deliveries were quite normal. In this case the child was delivered by forceps, and showed slight asphyxia which responded slowly, but no vigorous methods of resuscitation were employed. It is possible, however, that in all these cases the child may have sustained some mild injury at birth, even possibly hyperextension of the spine or compression of the chest, but sufficient to injure the lower part of the thoracic duct when it is specially fragile due to a congenital weakness or defect.

In all the neonatal cases the child appeared to be quite well to begin with, and then after an interval of time, varying between four and twenty-one days, developed a fairly sudden onset of dyspnoea due to rapid formation of a right-sided pleural effusion. It should be noted that in the cases where chylothorax follows a definite injury, there is always a delay before the sudden appearance of the pleural effusion. This delay is usually two to ten days, but may even be up to three weeks or longer. It is difficult to explain this interval of time, but it may be associated with the fact that the thoracic duct is anatomically extrapleural in position. It has been suggested that the interval represents the time required for erosion and perforation of the contiguous pleura by the enlarging retropleural collection of chyle. This suggestion would explain the delay in the onset of the development of the chylothorax in the neonatal cases if it is agreed that it is the result of an injury at birth.

The progress in these cases is interesting in that three of the cases recovered after simple repeated aspirations presumably by the spontaneous closure of the fistula. The case of Janet *et al.* (1936) recovered after one aspiration, that of Wessel (1944) after 13, and this case after two. In the adult, traumatic chylothorax has been treated successfully by the ligation of the thoracic duct (Baldbridge and Lewis, 1948), but this would be impossible in infantile cases. Repeated aspirations seem to be the only line of treatment, but should these have to be continued for a long time, then the maintenance of nutrition becomes essential but will be difficult owing to the persistent loss of fluid, fat, and protein.

Summary

A case of chylothorax in a neonate is described. Spontaneous recovery occurred after two aspirations. The aetiology is discussed, and it is concluded that the condition in neonates is most likely to be the result of a birth injury to the thoracic duct.

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RED CELL AND PLASMA VOLUME IN NEWBORN INFANTS

BY

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Schücking (1879) estimated the total blood volume of six newborn infants. In two infants, whose cords had been tied soon after delivery, blood volume was distinctly smaller than in four other infants whose cords had not been tied until some minutes after delivery. However, these estimates were made by Welcker's method and were by no means exact. The plasma volume of newborn infants was measured by Lucas and Dearing (1921) using brilliant vital red, with rather variable results. Robinow and Hamilton (1940), using the same method, found an inverse relationship between haematocrit and plasma volume, and noted that high blood volumes were slightly more common when the haematocrit was high. Estimations with the dye Evans blue were made by Brines, Gibson, and Kunkel (1941), and by Russell (1949), but both these studies were chiefly concerned with children rather than with very young infants.

A more extensive study of the plasma volume of newborn infants was made by DeMarsh, Windle, and Alt (1942), who were particularly concerned with demonstrating the effects on blood volume of early and late tying of the cord. Total blood volume was calculated from plasma volume and venous haematocrit. Their findings may be summarized as follows: in infants who were deprived of their placental blood by early clamping of the cord, the haematocrit did not rise after delivery; by contrast, in infants who recovered their placental blood, the venous haematocrit rose, on the average, from 51% to 61% within three hours of birth. The plasma volume three hours after birth was not significantly greater in infants recovering their placental blood than in those deprived of it—further evidence of the rapidity of the adjustment. Three days after birth the findings were substantially the same, that is, the average plasma volume in the two groups was almost identical but the venous haematocrit averaged 60% in those infants who had recovered their placental blood and was only 51% in those who had been deprived of it. There were considerable variations between individual estimates. For example, in one infant whose blood volume was estimated on the first and third days of life, the figure was 408 ml. on the first day and 243 ml. on the third day. That this difference in the estimates was largely to be ascribed to experimental error is suggested by the observation that the venous haematocrit was substantially the same on the two occasions. One is bound to conclude that the method of plasma volume estimation carried rather a large error.

Although the main conclusions of DeMarsh *et al.* on the effect of placental transfer appear to be soundly established, the figures for total blood volume published by them cannot be taken as a reliable guide to the true blood volume of newborn infants. It is now widely recognized that estimates of blood volume based on plasma volume and venous haematocrit are higher than the true values. Smith, Arnold, and Whipple (1921), who were perhaps the first to reach this conclusion, suggested that the discrepancy was due to the fact that the proportion of red cells was higher in large vessels than in the body as a whole.

Hahn, Balfour, Ross, Bale, and Whipple (1941), and Gibson, Peacock, Seligman, and Sack (1946) estimated red cell volume using red cells tagged with radioactive iron. They found that these direct estimates were always lower than those deduced from measurements of plasma volume and venous haematocrit. Gibson *et al.* concluded that the ratio

$$\frac{\text{'whole body haematocrit'}}{\text{venous haematocrit}}$$

was a constant, the term 'whole body haematocrit' being used to denote the relationship between the true red cell volume and the true total blood volume. Their conclusion was based on observations made on human subjects whose venous haematocrit ranged from 38·5% to 48·1% and on dogs whose

haematocrits ranged from 31% to 62% (only two above 53%).

It is evident that if the relationship of 'whole body haematocrit' to observed venous haematocrit is in fact a constant, it should be possible to measure total blood volume accurately simply by estimating plasma volume and venous haematocrit and then multiplying the venous haematocrit by the appropriate constant so as to discover the true red cell volume. It is to be noted that Gibson, Aub, Evans, Peacock, Irvine, and Sack (1947) and Ross, Finch, Peacock, and Sammons (1947) have stated that true red cell volume can be deduced from plasma volume and venous haematocrit in a different way. First,

$$\text{Blood volume} = \text{Plasma volume} \times \frac{100}{(100-H)}$$

where H = venous haematocrit.

then

Observed red cell volume = (blood volume) − (plasma volume);

this observed red cell volume is then multiplied by the 'constant' 0·85, to obtain the true red cell volume. Below, it will be demonstrated that this method of calculation is open to criticism.

At first sight it might appear that the true blood volume of normal infants could be discovered simply by recalculating the figures of DeMarsh *et al.* However, there are several reasons why this method could not be relied on to give precise answers. First, DeMarsh *et al.* found great variations in plasma volume from one case to another, suggesting a rather large experimental error. Secondly, even if it were true that the relationship of whole body haematocrit to observed venous haematocrit were constant in infants, as in adults, it could not be assumed that the constant had the same value in the two groups. Moreover, it cannot be assumed that the relationship between whole body haematocrit and venous haematocrit, which has been shown to apply in adults and dogs when the venous haematocrit ranges between 31% and 53% (or even to 62%), will continue to apply when the haematocrit rises to higher levels. For instance, the venous haematocrit of newborn infants may exceed 70%.

Thus it appeared that the best way to discover the true blood volume of infants was to measure plasma volume and red cell volume separately. By doing this, it was hoped not only to establish reliable figures for the blood volume of newborn infants, but also to determine the relationship between observed venous haematocrit and whole body haematocrit over a wide range. The study was closely linked with another piece of work proceeding simultaneously. This had as its object the determination of the rate of red cell exchange during replacement transfusions in infants affected with haemolytic disease of the newborn. Thus, although the majority of the infants tested were healthy, some were affected with haemolytic disease of the newborn.

Methods

Selection of Cases. Fifty-three newborn infants were tested; of these, 38 were healthy and 15 were affected with haemolytic disease of the newborn. However, seven of the latter infants were only mildly affected and had venous haematocrit values within the normal range.

Clinical Procedure. At the moment of birth a small sample of blood was taken from the umbilical cord, to be mixed with radioactive phosphorus as described below. In some cases the cord was tied immediately after birth and in others was not tied until the umbilical vein had almost collapsed; in these latter cases the taking of the sample was delayed so as to interfere as little as possible with the transfer of blood from the placenta to the infant.

Of the blood volume estimations, 70% were carried out within six hours of birth; only two of these estimates were made less than one and a half hours after birth. In the remaining 30% of cases the estimates were made when the infant was 6½-24 hours old. With careful aseptic precautions the umbilical cord was completely divided about 2 cm. from the abdominal wall and a 19-gauge pure polythene catheter, sterilized by boiling, was passed up the umbilical vein for a distance of 5-7 cm. After withdrawing about 1 ml. of blood to rinse the catheter, a new dry syringe was attached and a sample of 8 to 10 ml. was withdrawn. Then, through the same needle and catheter 1 ml. of a suspension of the infant's own red cells, prepared as described below, was injected from a calibrated syringe. After the injection blood was drawn back from the infant into the syringe and re-injected, and this washing-in was repeated about six times. Evans blue, 1 ml. (containing approximately 1 mg. of dye) was now washed in from another calibrated syringe in the same way. (The same two 1-ml. 'tuberculin' syringes were used throughout.) The catheter was now withdrawn. Approximately eight minutes later a new catheter was inserted and then, between nine and thirteen minutes after the injection, a sample was withdrawn, noting the precise time that had elapsed. As before, the catheter was first rinsed by withdrawing 1 ml. of blood before the sample (approximately 10 ml.) was obtained. The cord was now tied and dressed in the usual way. The procedure did not upset the infants at all and was not followed by any untoward sequelae. As a rule, the infant was not given penicillin as a prophylactic measure, and no infections were observed. In all cases the umbilical stump healed normally.

In 17 of the earlier cases a slightly different procedure was followed. No sample of blood was taken before the injection of the tagged red cells and dye, but two samples were taken afterwards, at 10 and 20 minutes respectively. In these cases the concentration of dye in the plasma was determined by Morris's chromatographic method (1944). A further difference in eight of these cases was that the dye and radiocative cells were injected in a larger volume of fluid (total 15 ml.).

Measurement of Plasma Volume. Plasma volume was measured by two methods, (*a*) direct, and (*b*) by extraction.

(*a*) DIRECT METHOD. The concentration of dye in the 10-minute plasma sample was measured in the photoelectric colorimeter, in cells with an optical thickness of 5 mm., using pre-injection plasma as a blank. The filter used was a combination of Ilford filters 803 and 205.* This filter is highly selective and traces of haemolysis do not cause appreciable errors. Nevertheless, in the one or two instances in the present series where samples were slightly haemolysed, the samples were discarded.

Standards were prepared in two ways: first, at the time of each blood volume determination, 20 c.mm. of the dye injection solution was pipetted into 3 ml. of the infant's pre-injection plasma (after using the latter as a blank in the colorimeter), to give a 1/151 dilution of the injection solution. These standards varied from one another by as much as 4%. It was demonstrated that the variation was mainly due to the irregular way in which T-1824 adhered to the walls of the capillary pipette rather than to any difference between plasma samples. The average value of the standards showed no tendency to rise or fall during the period of the experiments. It was considered that a more precise estimate of the standard could be obtained by making dilutions of Evans blue in plasma on a larger scale. Accordingly dye was delivered from the syringe used for injection into a volumetric flask. Various dilutions (in serum and plasma) were made and a calibration curve was obtained. It was noted that the relation between dye concentration in plasma and the optical density of the sample was substantially linear over the rather small range of concentrations encountered in this series. Therefore, finally, a standard galvanometer reading was taken as corresponding to a plasma volume of 150 ml. and all calculations of plasma volume were based on this figure. In fact this figure differed by only 1% from the average reading of all the small-scale standards referred to above.

(*b*) EXTRACTION METHOD. In some preliminary experiments dye was added to plasma and then eluted by Morris's chromatographic method (1944). The recovery of the dye was estimated and found, as claimed by Morris, to be virtually complete.

As a further check the plasma volume of a few infants (and adults) was measured by this method, and by the direct estimation of the dye in plasma; very satisfactory agreement was found. Accordingly, in a series of 17 infants the plasma volume was estimated by this method. The first 13 cases gave figures which seemed mutually consistent, but the next four results were much higher. In two of these latter cases the plasma volume was also estimated by a direct method and found to be some 20% lower than the estimates of the chromatographic method. It seemed certain that dye was being lost in the extraction process, and this was soon confirmed by a more extensive series of experiments *in vitro*. In these experiments the recovery of the dye was often complete, but in an appreciable proportion of cases the dye was not completely absorbed from the plasma when the samples were passed through the aluminium hydroxide column. The difficulty was not overcome by substituting many different samples of $Al(OH)_3$, nor by adopting the modified procedure recommended by Hecht and Greenberg (1948); we did not, however, succeed in obtaining the brand of $Al(OH)_3$ recommended by the latter workers. It had thus to be concluded that in our hands the results of the chromatographic method could not be considered consistently reliable.

In the cases in which dye concentration was measured by the chromatographic extraction method, standards were prepared in two ways: either by injecting dye into a known volume of plasma from the syringe used in the estimation and then putting 2 ml. aliquots through the extraction process; or by pipetting small quantities of dye into known volumes of ' eluent B '.

Dye Loss. It was recognized that by taking only one sample of plasma, 10 minutes after the injection of the dye, some error would be introduced because of variable losses of dye from the circulation in individual cases. Noble and Gregersen (1946) found that in adults estimates based on a single sample taken 10 minutes after injection nearly always gave values between -2% and $+4\%$ of the ' true ' values, that is to say, the values calculated from extrapolation of the disappearance curve after mixing was complete.

Data obtained from our red cell volume estimates showed that in newborn infants mixing of red cells is virtually complete within 10 minutes of the injection. It is possible that mixing of the plasma is a little slower since it is known that red cells circulate more rapidly than does plasma (Freis, Stanton, and Emerson, 1949). But it seems likely that mixing of the plasma is at least very nearly complete at 10 minutes. Estimates of the rate of dye loss in newborn infants were obtained in two different ways: firstly, in those infants from whom samples were taken 10 and 20 minutes after injection and in whom dye concentration was measured by the extraction method. In these cases dye concentration was on the average 3% lower in the 20-minute samples than in those taken at 10 minutes. Secondly, in other cases, two or three plasma samples were taken during the few hours following injection; the estimates were corrected for the effect of haemodilution if any significant changes in haematocrit occurred. From these experiments it was concluded that the rate of dye loss in newborn infants is of the order of 20% per hour, and is thus appreciably higher than in adults. Accordingly, it is probable that during the 10 minutes after injecting the dye into infants, there is a loss of some 3% to 4% compared with 1% to 2% loss in adults during a similar period. If plasma mixing is complete at the end of 10 minutes, in the newborn infant, as it is in the adult, estimates based on the dye concentration of the 10-minute sample will thus tend to be, say, 3% too high, but any extra slowness in mixing in the newborn infant would cause an error in the opposite direction. Since it was not feasible to make direct measurements to estimate the mixing time in newborn infants, and since it appeared that in any case the correction involved would be a

* We are grateful to Professor E. J. King for suggesting the use of these filters.

small one, it was decided to make no correction and to base all estimates of plasma volume on the dye concentration of the sample taken 10 minutes after injection.

One further point to consider is the possibility that after withdrawing such a relatively large amount of blood as 10 ml. from an infant, some haemodilution may occur, even during the subsequent 10 minutes. If this did occur, it would obviously introduce a further error into the calculation. However, the average change in venous haematocrit 10 minutes after withdrawing 10 ml. of blood, in 21 infants in whom observations were available, was found to be only $-0{\cdot}3$ division on the haematocrit scale. At first sight this might appear to be evidence of slight haemodilution, but it must be remembered that when a venous blood sample is taken the blood removed is not strictly representative of the blood in the whole body but contains a higher proportion of red cells. Thus, even if there is no increase in plasma volume after withdrawing a blood sample, there will be a small fall in venous haematocrit as soon as the adjustment is complete. The extent of the fall expected in this particular series was calculated, using data described below, and was found to be $0{\cdot}3$ on the haematocrit scale. It was thus concluded that the very small fall in venous haematocrit observed was not evidence of any significant replacement of plasma following the withdrawal of the 10 ml. sample. The plasma volume before taking the first blood sample was calculated by estimating the plasma volume 10 minutes after injection and adding to this figure the amount of plasma removed in the first blood sample.

In eight of the cases in which plasma volume was estimated by the extraction method for Evans blue, the dye and radioactive cells were injected in a volume of approximately 15 ml. In estimating the pre-injection volume in these cases, a correction was applied on the assumption that the fluid was retained in the circulation during the 10 minutes after injection. Evidently this may have added to the error of these estimates, and it should be made clear that the main conclusions of this paper do not depend on this series of estimates. Plasma volume was estimated by the direct method in a further 25 infants, and all the conclusions reached in this paper can be supported on this evidence alone. Nevertheless, the first 13 estimates of plasma volume made by the extraction method do not appear to be inconsistent with the remaining data, and they have therefore been included; these observations are specially marked in the tables and figures.

Determination of Red Cell Volume with Radioactive Phosphorus. The method used was essentially the same as that described by Reeve and Veall (1949), with only minor modifications. About 5 ml. of the infant's blood were incubated with 5 to 10 micro-curies* of P^{32} for 30 to 45 minutes, so that, after washing, the red cells contained about 1 micro-curie of P^{32}. After the red cells had been washed the volume of saline suspension was adjusted to 5-10 ml. Of this suspension 1 ml. was injected into the infant and 1 ml. was used for the preparation of a standard 1/100 dilution. Consequently, the P^{32} dose was $0{\cdot}1$ to $0{\cdot}2$ micro-curies in the form of labelled red cells.

Syringe calibration tests *in vitro* using a labelled red cell suspension showed that with the syringe selected for these experiments it was possible to inject 1 ml. of radioactive red cell suspension with an error of less than 1%.

The blood samples were taken into dry, heparinized 10 ml. graduated centrifuge tubes. After removal of sufficient blood for haematocrit determination, the tubes were covered with a cellophane cap and centrifuged at 3,000 r.p.m. for 20 to 30 minutes. The volume of the blood sample could then be read to within $\pm 0{\cdot}05$ ml. The supernatant plasma was removed for dye estimation, and sufficient phosphate-citrate buffer solution was then added to the packed red cells to bring the volume of the sample to 10 ml. After lysing the red cells with saponin, the P^{32} content of each sample was compared with that of the standard by means of a liquid sample counter (Veall, 1948). After correcting for dilution, haematocrit and P^{32} loss from the red cells *in vivo*, the P^{32} content per ml. of red cells was obtained. The amount of P^{32} injected could be determined from the value of the standard solution, and thus the infant's red cell volume could be calculated. The correction for P^{32} loss was the same as that used by Reeve and Veall in their work on adults, i.e. +1% for a 10-minute sample, +2% for a 20-minute sample, etc. In a number of cases two or more samples were obtained from the infant, usually at 10 and 20 minutes after injection of the labelled red cells, and no significant difference was found between the figures for red cell volume calculated from these two samples. Consequently, it would appear that no appreciable error is introduced by assuming that the rate of loss of P^{32} from red cells is approximately the same in infants as it is in adults.

Radiation Dosage. The question of radiation dosage received by the patient when this method is used for the determination of red cell volume is discussed in detail by Reeve and Veall (1949). In the present experiments the amount of P^{32} used was less than $0{\cdot}1$ micro-curie per kg. body weight. Assuming that all the injected P^{32} remains in the blood stream for the first 24 hours after injection, and assuming a blood volume of 85 ml./kg., the blood and the immediate environs of the vascular system would receive a radiation dose of $0{\cdot}049$ equivalent roentgens (r.) in 24 hours. This can be regarded as the absolute maximum dose received by any organ in the body in any one day, and is certainly an overestimate. The loss rate of P^{32} from the blood is such that about half of it has disappeared in 24 hours, to be distributed around the body or excreted. This figure may be compared with that for the maximum permissible daily radiation dose of $0{\cdot}1$ r., which is currently accepted (M.R.C., 1949) for those who encounter radiation hazards every working day throughout their life. Alternatively, if the radio phosphorus is considered to have been redistributed and fixed uniformly all over the body, then, neglecting excretion, the tissues would receive a total dose of $0{\cdot}087$ r. during the radioactive life of the P^{32}, spread

* The P^{32} was supplied partly by Oak Ridge National Laboratories, U.S.A.E.C., and partly by the Atomic Energy Research Establishment, Harwell, through the M.R.C. The quantities were measured in terms of the micro-curie adopted by the M.R.C. as the standard of activity for P^{32} for the year 1949.

over several weeks. It is known that P^{32} is selectively taken up by certain tissues, though probably not in excess of about six times the average body concentration. Such tissues would thus receive a total of about 0·5 r., again spread over several weeks. This appears to be of the same order as the dose received by the foetus when a single radiograph is taken during pregnancy, or the skin dosage received as a result of an ordinary diagnostic x-ray film (Martin, 1947). In any case, even in an organ in which the concentration was six times the average throughout the body, the maximum dose rate would be the initial one of 0·024 r. per day, which is still considerably less than the maximum permissible daily dose. Thus, the radiation hazard of this method of investigation is no greater, and is almost certainly less, than that of a single routine x-ray examination.

Determination of Red Cell Volume by the Ashby Method. In five cases red cell volume was determined by the Ashby method as modified by Barnes, Loutit, and Reeve (1948). Some further modifications were necessary to make the method suitable for use in infants. Three of the infants tested were affected with haemolytic disease of the newborn and were transfused with Rh negative blood; the fourth infant was transfused because it was found to be pale and cold after birth and it was considered that it would benefit by transfusion. In each of the five cases approximately 10 ml. of the infant's blood was first removed and then an accurately measured amount (40-50 ml.) of fresh blood of suitable group was injected from an all-glass 50 ml. syringe over a period of some 10 or 15 minutes. These manipulations were carried out through a polythene catheter passed up the umbilical vein. Five to ten minutes after the end of the injection a fresh catheter was passed and a sample of blood obtained. The concentration of donor red cells in the post-transfusion blood sample was estimated by differential agglutination using anti-A or anti-M serum. The red cell volume of the infant after transfusion was calculated from the formula given by Barnes *et al.* (1948). The red cell volume before transfusion was then calculated by deducting the volume of red cells injected and adding the volume of red cells removed in the first blood sample. In making the red cell counts, both on the donor blood sample and on the infant's post-transfusion samples, not less than 2,000 red cells were counted.

Venous Haematocrit. The venous haematocrit was determined by centrifuging blood samples in ordinary Wintrobe haematocrit tubes; the tubes were spun for 30 minutes at 3,000 r.p.m. in a centrifuge of 15 cm. radius. Following Barnes *et al.* (1948), all observed readings were multiplied by the factor 0·95 to correct for trapped plasma and thus to give a true estimate of the volume of red cells in the sample. For the estimation of red cell volume, it was necessary to determine the height of the red cell column in the haematocrit tube, rather than the total height of the cell column. In practice this was sometimes difficult because the separation between red cells and white cells was often not so sharp as in the adult haematocrit. Often there were two layers above the red cell column, the lower of the two being pink and the upper white. The pink layer was sometimes not separated from the main red cell column by any sharp dividing line. Since the upper layer usually occupied only about 0·5 of a division, whereas the pink layer occupied one or two divisions, and the leucocyte count is known to be considerably higher in the infant than in the adult, it was considered that the subtraction of only 0·5 from the total height of the column would not give a fair estimate of the red cell volume. Moreover, direct microscopic examination showed that the pink layer was in fact a mixture of red and white cells. It was decided that the most satisfactory method of dealing with this difficulty was to subtract 2·0 from the total height of the column in all cases, whether or not the dividing lines seemed to be sharp. Thus the true volume of red cells in all venous samples was calculated from the formula $(P.C.V.-2)\times 0\cdot 95$, packed cell volume (P.C.V.) being the total height of the cell column in the venous haematocrit. In all the tables and figures in this paper, the term ' venous haematocrit ' is used for this estimate of the proportion of red cells in unit volume of venous blood.

Results

All measurements of plasma volume and red cell volume are recorded in Table 1, together with various deductions from the data. The cases are arranged in order of venous haematocrit.

Plasma Volume. In Fig. 1 estimations of plasma volume, expressed in ml./kg., have been plotted against venous haematocrit. The cases appear to fall into two groups.

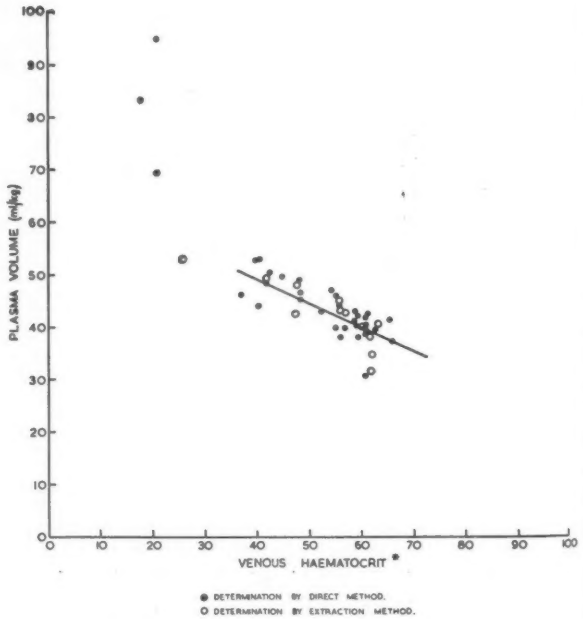

FIG. 1.*—Estimates of plasma volume in 46 newborn infants, plotted against venous haematocrit. The regression line has been calculated from data relating to the 34 normal infants; the slope of the line= $-0\cdot 454 \pm 0\cdot 008$.

(1) Almost all the observations fall in the haematocrit range 37 - 66·2, and in this range there is a slight but steady fall in plasma volume as haematocrit rises. The regression line drawn in Fig. 1 has been calculated from data applying to 34 normal infants only, and it will be noted that the slope of the line is some 50 times its standard deviation. If the 34 normal infants are divided into two groups, those with a venous haematocrit of 59·3 - 66·2 are found to have an average plasma volume of 38·6 ml./kg. (standard error of mean=0·81), and those with haematocrits ranging from 39·9 - 58·5 have an average plasma volume of 44·1 ml./kg. (S.E. of mean=0·88).

(2) The four most anaemic infants (haematocrit range 17·9 - 21·2) had much greater plasma volumes; all four infants were found to have an increased venous pressure and were considered to be in cardiac failure (Mollison and Cutbush, 1949).

The time after birth at which plasma volume was estimated did not appear to affect the results significantly. The estimates made within three hours, and even within two hours, were distributed about the regression line in the same way as the estimates made later after birth.

Red Cell Volume. In Fig. 2 observed red cell volume in ml./kg. is plotted against venous haematocrit. It appears that the relationship is substantially linear up to a certain haematocrit level—approximately 55—but that above that level the venous haematocrit does not accurately reflect the true red cell volume.

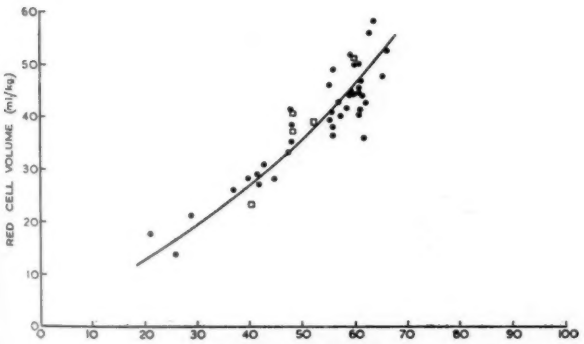

FIG. 2.*—Estimates of red cell volume (ml./kg.) in 43 newborn infants plotted against venous haematocrit. The line is not a calculated regression line but merely indicates the trend of the data.

Total Blood Volume. Total blood volume was calculated by adding together observed red cell volume and plasma volume and multiplying the total by the factor 1·02. This correction had to be applied to take into account the volume of leucocytes in the circulation. It will be remembered that, throughout, red cell volume was estimated from the formula (P.C.V.−2)×0·95. All estimates for total blood volume in ml./kg. are plotted against venous haematocrit in Fig. 3.

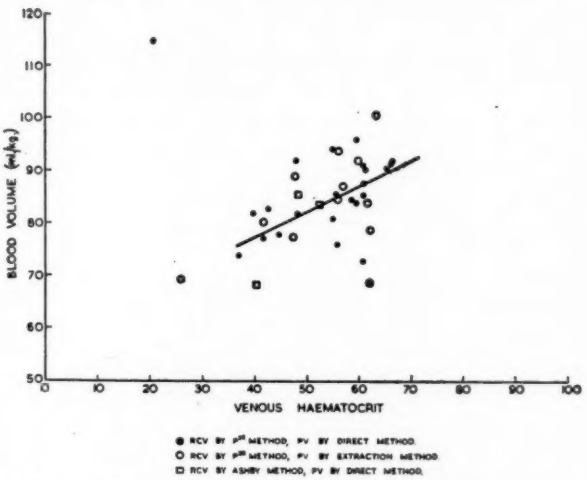

FIG. 3.*—Estimates of total blood volume (ml./kg.) based on separate estimates of plasma volume and red cell volume in 37 newborn infants, plotted against venous haematocrit. The regression line has been calculated from data relating to the 28 normal infants; the slope of the line = 0·4791 ± 0·3841 (not significant).

One infant had a much higher blood volume than any of the others. This was one of the four infants in cardiac failure, mentioned above; in the other three of these infants either the red cell volume or the infant's weight was not known so that comparisons were impossible. The remaining cases show a tendency for blood volume to increase as venous haematocrit rises; however, the slope of the regression line in this series is not quite significant (only $1\frac{1}{2} \times$ S.D.).

Twenty-eight of the infants whose total blood volume was estimated were normal. (Cases of haemolytic disease, however mild, are excluded from this group.) The average blood volume of these infants was found to be 84·7 ml./kg. Since the majority of these cases had haematocrits above the range for normal adults (average of the group =56·8), it was considered interesting to select infants whose venous haematocrit fell within the adult range and to compare red cell volume and

No.	Normal (N) or Haemolytic Disease (D)	Weight (kg.)	Corrected Venous Haematocrit‡	Red Cell Volume		P
				ml.	(ml./kg.	ml.
1	N	4·41	66·2	231	52·5	164
2	N	2·97	65·6	141	47·5	122
3	N	3·97	63·3	230	57·8	161†
4	N	3·56	62·5	198	55·6	—
5	N	3·97	62·7	—	—	156·5
6	N	3·18	62·3	134·5	42·3	110†
7	N	3·15	62·0	112	35·6	98†
8	N	2·82	61·7	124	43·8	108†
9	N	3·93	61·3	161	40·9	—
10	N	3·12	61·3	—	—	132
11	N	3·41	61·2	159	46·7	143
12	N	3·94	61·0	159·5	40·5	120·5
13	N	3·94	60·9	176	44·6	153
14	N	3·20	60·9	159	49·8	126
15	N	3·78	60·9	171	45·2	153
16	N	3·72	60·0	185	49·8	149†
17	D	3·09	59·9	157*	51·0	—
18	N	4·01	59·6	178	44·4	151·5
19	N	3·77	59·4	194·5	51·6	159·5
20	N	3·34	59·4	144	43·2	—
21	N	3·45	59·3	—	—	139
22	N	4·00	58·8	—	—	172
23	N	4·11	58·7	170	41·4	169
24	N	2·76	57·4	111	39·9	—
25	N	3·77	57·0	—	—	149·5
26	N	3·68	57·0	157	42·6	156·5
27	N	3·30	56·2	161	48·8	142†
28	N	2·91	56·0	105	36·1	110·5
29	N	3·07	55·9	116	37·9	138†
30	N	2·95	55·7	120·5	40·8	130·5
31	N	4·52	55·2	176·5	39·1	180·5
32	N	3·91	55·2	179·5	45·9	180
33	N	3·72	54·4	—	—	174
34	D	2·95	52·4	114*	38·7	127
35	N	3·63	48·4	127	35·0	164
36	N	3·22	48·4	119*	37·0	150
37	D	3·44	48·1	141·5	41·2	168
				139·5*	40·5	
38	D	2·50	47·8	95·5	38·2	120
39	N	2·75	47·5	91·0	33·1	116
40	D	3·31	44·8	92·5	27·9	164
41	N	3·72	42·6	113·5	30·6	187
42	D	2·55	41·8	72	28·3	123
43	D	3·18	41·7	92	28·9	157
44	D	3·52	40·7	—	—	186
45	N	3·20	40·2	73·5*	23·1	140
46	N	3·56	39·9	99	27·8	187
47	D	2·90	37·0	75	25·9	134
48	D	2·81	28·9	59	21·0	—
49	D	2·27	25·9	33·5	14·7	120
50	D	3·6	21·2	—	—	249
51	D	2·63	21·1	46·5	17·7	249
52	D		19·9	49	—	222
53	D	3·10	17·9	—	—	258

Plasma Volume		Blood Volume (ml./kg.)	Body Haematocrit	Body Haematocrit / Venous Haematocrit	Red Cell Volume calculated from P.V. and Haematocrit	"Error" %
ml.	(ml./kg.)					
164	37·2	91·3	57·5	·869	227·6	− 1·5
122	41·2	90·4	52·6	·802	167·2	+18·6
161†	40·5	100·3	57·6	·909	200·6	−12·8
—	—	—	—	—	—	—
156·5	39·4	—	—	—	—	—
110†	34·6	78·5	54·0	·868	134·3	− 0·2
98†	31·6	68·5	52·1	·840	118·3	+ 5·6
108†	38·3	83·7	52·3	·848	128·4	+ 3·5
—	—	—	—	—	—	—
132	42·3	—	—	—	—	—
143	41·9	90·3	51·7	·845	168·8	+ 6·2
120·5	30·6	72·5	55·9	·917	140·0	−12·2
153	38·8	85·0	52·4	·861	177·7	+ 1·0
126	39·4	90·8	54·8	·900	145·4	− 8·6
153	40·5	87·3	51·8	·852	177·0	+ 3·5
149†	40·0	91·6	54·4	·907	167·7	− 9·3
—	—	—	—	—	—	—
151·5	37·8	83·8	53·0	·888	166·3	− 8·6
159·5	42·3	95·8	53·9	·908	175·3	− 9·9
—	—	—	—	—	—	—
139	40·2	—	—	—	—	—
172	43·0	—	—	—	—	—
169	41·2	84·3	49·1	·847	180·4	+ 6·1
—	—	—	—	—	—	—
149·5	39·7	—	—	—	—	—
156·5†	42·6	86·9	49·0	·860	157·7	+ 0·4
142†	43·0	93·6	52·2	·928	137·6	−14·5
110·5	38·0	75·6	36·4	·829	107·7	+ 2·6
138†	45·0	84·6	44·8	·803	133·6	+15·0
130·5	44·2	86·7	47·1	·847	125·0	+ 3·7
180·5	39·9	80·6	48·5	·878	169·6	− 4·0
180	46·1	93·9	48·9	·886	169·2	− 5·8
174	46·8	—	—	—	—	—
127	43·1	83·5	46·4	·886	109·5	− 3·9
164	45·2	81·7	42·8	·885	119·5	− 5·9
150·5	46·7	85·4	43·3	·895	111·4	− 6·4
168·5	49·0	91·9	44·8	·933	123·9	−12·4
120†	48·0	88·7	43·1	·902	87·2	− 8·7
116·5†	42·5	77·1	42·9	·905	83·8	− 7·9
164·5	49·7	79·1	35·3	·788	107·5	+16·2
187	50·3	82·5	37·1	·872	112·5	− 0·9
123·5	48·4	78·0	36·3	·870	71·9	nil
157†	49·4	79·9	36·2	·868	91·0	− 1·1
186	52·8	—	—	—	—	—
140·5	43·9	68·0	34·0	·847	76·7	+ 4·4
187	52·6	81·9	34·0	·853	101·3	+ 2·3
134	46·2	73·6	35·2	·952	64·8	−13·6
—	—	—	—	—	—	—
120†	52·9	69·0	21·3	·823	35·8	+ 7·2
249	69·2	—	—	—	—	—
249	94·8	114·8	15·4	·730	56·6	+21·5
222†	—	—	17·9	·900	47·3	− 3·5
258	83·1	—	—	—	—	—

* Red cell estimate by Ashby method.
† Plasma volume estimate based on extraction method.
‡ (P.C.V.−2)×·95; see text.

plasma volume in such infants with published figures for adults. For comparison with the figures of Reeve and Veall, which refer to 13 adults with venous haematocrits ranging from 38·1-47·2 (average haematocrit 42·5), nine infants with haematocrits ranging from 37·0 to 47·5 (average 42·6) were selected; five of these infants had haemolytic disease of the newborn, but none appeared to have any disturbance of the circulation. In Table 2 the results of these estimations are set out, together with figures calculated from the published data of Reeve and Veall (1949) and Gibson *et al.* (1946).

It will be noted that for a comparable level of venous haematocrit, red cell volume and plasma bear the same relationship to body weight in infants as they do in adults.

Body Haematocrit. 'Whole body haematocrit' was calculated by dividing observed red cell volume by calculated total blood volume, determined as described above. This value was divided by the venous haematocrit, that is (P.C.V.−2)×0·95, to obtain the ratio

$$\frac{\text{body haematocrit}}{\text{venous haematocrit}}$$

and this ratio is to be found in column 11 of Table 1. In Fig. 4 body haematocrit is plotted against venous haematocrit, and it is evident that this relationship is a constant over the haematocrit range 17·9-66·2. Moreover, the extrapolated line passes through the origin. The value of the constant in this series was 0·868. This figure is the average for 38 cases, and analysis showed that the value

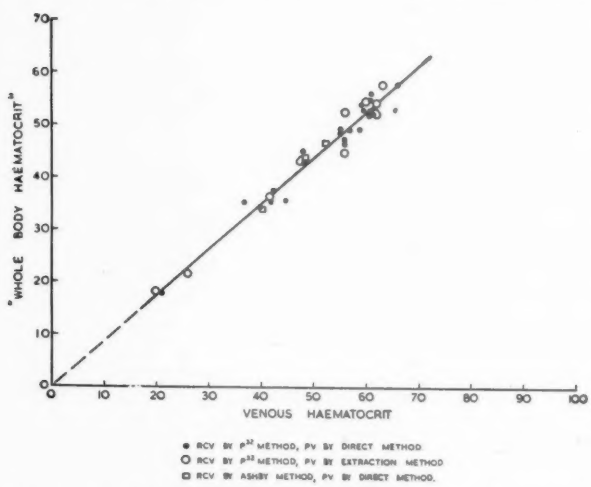

FIG. 4.*—'Whole body haematocrit' plotted against venous haematocrit in 38 newborn infants.

was not significantly affected by the method of determining plasma volume. The detailed results were as follows:

No. of Cases	Method of Estimating		Average Value of Constant
	Plasma Volume	Red Cell Volume	
22	Direct	P^{32}	0·863
13	Extraction	P^{32}	0·872
3	Direct	Ashby	0·876

Discussion

The average figure for plasma volume in 34 normal infants was 41·3 ml./kg.; this group of infants had an average weight of 3·55 kg. and an average venous haematocrit of 56·9. These figures may be compared with those for 17 infants tested on the first day of life by DeMarsh *et al.* Their infants had an average weight of 3·33 kg. and an average haematocrit of 57·0; there is no mention in their paper of any correction of venous haematocrit for trapped plasma, and thus it is probable that the figure of 57·0×0·95, or 53·7, should be taken as the average haematocrit for purposes of comparison. Thus the infants tested by them probably had a slightly lower venous haematocrit and would have been expected to have a slightly higher plasma volume: the average plasma volume of 42·7 ml./kg. in their 17 cases is thus in good agreement with our series.

As mentioned above, the present estimates of plasma volume are based on the dye concentration in samples taken 10 minutes after injection; and the assumption has been made that dye-loss is to some extent counterbalanced by incomplete mixing. If, in fact, mixing is complete in 10 minutes, all the estimates of plasma volume would have to be reduced by about 3%. However, in view of the absence of any reliable data about the mixing time of T-1824 in the plasma of newborn infants, we have preferred not to apply any correction factor.

DeMarsh *et al.* divided their cases into two groups, namely those whose cords were clamped early, and those whose cords were clamped late. The latter group had an average haematocrit of 61% compared with an average of 51% in the group deprived of the placental blood. Plasma volume averaged 43 ml./kg. (S.D. 7·4) in the first group and 42 ml./kg. (S.D. 8·8) in the second group, so that no relationship between venous

* In Figs. 1–4 the term "venous haematocrit" is used for an estimate of the true volume of red cells in unit volume of venous blood; this estimate is based on the formula: (P.C.V. −2) × ·95, where P.C.V. = total packed cell volume in the venous haematocrit, −2 is an average correction for leucocytes and × ·95 is a correction to account for trapped plasma.

haematocrit and plasma volume could be demonstrated. Nevertheless our data indicate that plasma volume does fall as venous haematocrit rises; and the error of our estimates is sufficiently small to make it possible to demonstrate that this relationship is significant.

Fig. 2 shows that the relationship between red cell volume and venous haematocrit is substantially linear up to venous haematocrit values of approximately 55%, but that at higher haematocrit levels the red cell volume increases disproportionately. Hahn and Bale (1942) found a linear relationship between red cell volume and venous haematocrit, but did not test cases with haematocrits greater than 55%.

Fig. 3 suggests that blood volume rises with venous haematocrit, but this question is not settled decisively by our data, presumably because the errors of both the plasma volume estimation and red cell volume estimation are concerned. However, from the consideration that plasma volume presumably cannot fall to zero, it follows that at some point blood volume must start to increase with haematocrit. In practice it appears that blood volume increases with haematocrit throughout the range studied.

Fig. 4 shows a rather smaller scatter round the correlation line than do the other curves, and this may be due in part to the fact that the expression 'whole body haematocrit' is independent of body weight.

It will be noted that the value of the ratio

$$\frac{\text{'whole body haematocrit'}}{\text{venous haematocrit}}$$

is 0·87 (0·868) in this series. This figure compares closely with that of 0·91 reported by Gibson, Peacock, Seligman and Sack (1946), in human adults and in dogs. The discrepancy between the two series may be a little smaller than it at first appears, because Gibson *et al.* calculated body haematocrit from the formula

$$\frac{\text{Red cell volume}}{\text{(red cell volume)} + \text{(plasma volume)}}$$

whereas in the present series the denominator was increased slightly to take the leucocytes into account. Nevertheless, in adults this correction would be a very small one, and would in any case not have reduced the figure of Gibson *et al.* to below 0·90.

It must be noted that our figure for this constant would be slightly too low if our estimates of plasma volume were too high. As mentioned above, it is possible that our estimates of plasma volume ought to be corrected by −3%, and one can calculate that this would raise the value of the constant to 0·886. In view of the possible effect of other systematic errors, it cannot be considered that any difference between adults and newborn infants, with respect to the value of this constant, has been demonstrated.

Gibson *et al.* (1946) found that the ratio of (true red cell volume) to (red cell volume deduced from plasma volume and venous haematocrit) varied from 0·70 to 0·95 (average 0·845) in a group of normal males. They appear to have assumed that this figure is also a constant in normal subjects. Gibson, Aub, *et al.* (1947) have stated that red cell volume can be deduced from estimates of plasma volume and venous haematocrit as follows: total blood volume is first calculated from plasma volume and venous haematocrit. Plasma volume is now subtracted from total blood volume to give 'observed red cell volume.' This figure is now multiplied by 0·85 to give the true red cell volume. Gibson, Aub, *et al.* (1947) and Ross *et al.* (1947) have made use of this 'correction' to determine the red cell volume. However, it can easily be shown that the ratios

(1) $\dfrac{\text{Body haematocrit}}{\text{Venous haematocrit}}$ and

(2) $\dfrac{\text{(True red cell volume)}}{\text{(Red cell volume deduced from plasma volume and venous haematocrit)}}$

TABLE 2

	Average Venous Haematocrit	Red Cell Volume (ml./kg.)	Plasma Volume (ml./kg.)	R.C.V. plus P.V. (ml./kg.)
Reeve and Veall (1949): 13 adults with venous haematocrit 38·1-47·2 ..	42·5*	30·0	46·6	76·6
Gibson et al. (1946): 40 adults with venous haematocrit 38·5-48·1 ..	42·4†	29·7	47·8	77·5
Present Series: 9 infants with venous haematocrit 37·0-47·8 ..	42·6*	29·2	47·9	77·1

* = Observed red cell haematocrit × ·95. † = uncorrected red cell haematocrit.

cannot both be constants, when red cell volume is deduced in this way. A simple concrete example is perhaps the clearest way of illustrating this point:

Assumption: $\frac{\text{Whole body haematocrit}}{\text{Venous haematocrit}} = k(=0\cdot9)$

Examples	A	B
True blood volume	100	100
True red cell volume	20	80
True plasma volume	80	20
Whole body haematocrit	20	80
Venous haematocrit	$\frac{20}{0\cdot9} = 22$	$\frac{80}{0\cdot9} = 89$
I. Blood volume from plasma volume and venous haematocrit	$80\times\frac{100}{78} = 102\cdot5$	$20\times\frac{100}{11} = 182$
II. Red cell volume (from I and plasma volume)	$102\cdot5-80 = 22\cdot5$	$182-20 = 162$
III. True red cell volume / Red cell volume (II)	$\frac{20}{22\cdot5} = 0\cdot89$*	$\frac{80}{162} = 0\cdot49$*

* This is the value which Gibson *et al.* (1946, 1947), have apparently assumed to be a constant.

Evidently the error in assuming that the ratio of true red cell volume to ' deduced red cell volume ' is a constant will be much less serious over a narrow range of haematocrit values than in the extreme examples used above.

Calculation of Blood and Red Cell Volume from Plasma Volume and Body Haematocrit. If the total blood volume is to be calculated from estimates of plasma volume and venous haematocrit it may be calculated as follows.

The observed packed cell volume (that is, total height of red cells plus white cells in the venous haematocrit) is first corrected by the factor 0·95 to allow for plasma trapped in the cell column, and this figure is then multiplied by 0·87* to obtain the true proportion of cells present in unit volume of blood in the body as a whole. The true proportion of plasma in the blood is then obtained by subtracting this figure from 100; this proportion may be expressed briefly as the ' body plasmatocrit.'

i.e. body plasmatocrit $= 100-0\cdot87(\text{P.C.V.}\times0\cdot95)$
$= 100-(\text{P.C.V.}\times0\cdot825)$

when P.C.V. = total height of cell column in the venous haematocrit

Then Blood Volume $= \frac{\text{Plasma volume}}{\text{Body plasmatocrit}} \times 100$

Similarly, red cell volume
$= \frac{\text{Plasma volume} \times \text{body red cell haematocrit}}{\text{Body plasmatocrit}}$

In the last two columns of Table 1 are to be found, first, red cell volume calculated from plasma volume and haematocrit, using the above formula, and second the ' error ' of the estimation; that is to say, the percentage deviation from estimations of red cell volume made with labelled red cells. The coefficient of variation of the calculated red cell volumes was found to be 8·8%; it is to be noted that this ' error ' includes the error of estimating red cell volume with labelled red cells, as well as the error of estimating plasma volume. Moreover, it takes no account of biological variation.

Assuming that the experimental errors of measuring plasma volume and red cell volume are similar, the error of deducing red cell volume from plasma volume and venous haematocrit using the above formula, becomes $\frac{8\cdot8}{\sqrt{2}}$ = approximately ±6%.

* This figure for the constant is valid for plasma volume estimates in newborn infants based on the dye concentration in a 10-minute sample, uncorrected for possible errors due to incomplete mixing or loss of dye. If further work should show that the true plasma volume is some 3% lower than the figure thus obtained, the formula for the ' body plasmatocrit ' would become $100-\cdot886(\text{P.C.V.}\times0\cdot95)$, or $100-(\text{P.C.V.}\times0\cdot84)$.

Summary

Estimations of plasma volume (using T-1824) or red cell volume (using labelled red cells) have been made in 53 newborn infants, of which 38 were normal and 15 affected with haemolytic disease of the newborn. In 38 infants both plasma volume and red cell volume were estimated.

In 34 normal infants the average plasma volume was 41·3 ml./kg. However, plasma volume was not independent of haematocrit but on the contrary rose steadily throughout the venous haematocrit range 66·2 - 37·0. In four infants with haematocrits between 17·9 and 21·2, plasma volume was disproportionately raised, but these infants were in cardiac failure.

Red cell volume was measured in 44 infants. The relationship between venous haematocrit and red cell volume was approximately linear when the venous haematocrit was below 55%. However, above this level the venous haematocrit did not rise proportionately to the true red cell volume.

The total blood volume of 28 normal newborn infants, deduced from measurements of plasma volume and red cell volume, was 84·7 ml./kg. On theoretical grounds blood volume is expected to increase with venous haematocrit, but this relationship could not be demonstrated conclusively in the present cases.

The ratio of the 'whole body haematocrit,' that is

$$\frac{\text{total red cell volume}}{\text{total blood volume}}$$

to the venous haematocrit was found to be a constant in the venous haematocrit range 17·9% - 66·2%. The value of the constant in this series was 0·87.

Provided that the venous haematocrit is first multiplied by this constant, estimates of red cell volume obtained by the dye-haematocrit method agree satisfactorily with estimates made by labelled red cell methods.

The work described in this paper was carried out in the Institute of Obstetrics and Gynaecology and the Institute of Child Health at the Postgraduate Medical School of London. We should like to thank Professor James Young and Professor A. A. Moncrieff for facilities, and members of their staffs for help of many kinds.

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TECHNICAL PROBLEMS IN METABOLIC INVESTIGATIONS IN CHILDHOOD

BY

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(Received for Publication November 23, 1949)

The great difficulty encountered in obtaining accurate collections of faeces and urine from young children is common knowledge to all those engaged in metabolic investigation on these subjects. It was therefore thought worth while recording the methods that we have found most satisfactory to date.

Problems of Collection

While older children present no greater problem than adults, in that they will cooperate fully in making the required collections, younger children are unreliable and require special appliances.

The most generally useful of these is the metabolic bed. Various types of such a bed have been described (Bendix, 1896; Bendix and Finkelstein, 1900; Schabad, 1908; Talbot, 1909; Du Bois, 1911; Howland and Cooke, 1911; Hoobler, 1912; Gerstley, 1930; Hoag, 1932) and others all write of metabolic beds. These beds differ widely in construction and detail, but the principle of all of them, and of the one described below, is the same. The latter was devised because the materials used were easily obtainable and it could be made in the hospital. The basic idea was taken from the metabolic bed used at the Belle Vue Hospital, New York. It was made from an old empyema frame, appropriate holes being cut for faeces and urine to pass through into suitable receptacles placed below. In the case of the urine, this was made possible by using a glass urinal which was connected by rubber tubing to a bottle placed underneath the cot.

The Metabolic Bed

The bed with a child lying in it is illustrated in Plate I.

There should be a round hole 5 in. in diameter about two-thirds of the way from the head of the frame (Fig. 1). (It is advisable to strengthen the canvas round this by lines of machine stitching and over-sewing the edge.) A slit 4 in. long and 2 in. wide is made in the midline below the round hole, and separated from it by about 2 in. Similar holes to correspond must be made in the sheets used. The frame is placed on the cot in a sloping position, the upper end resting in the sockets for the half-way position of the cot sides, and the lower end resting on the springs. The mattress is not used.

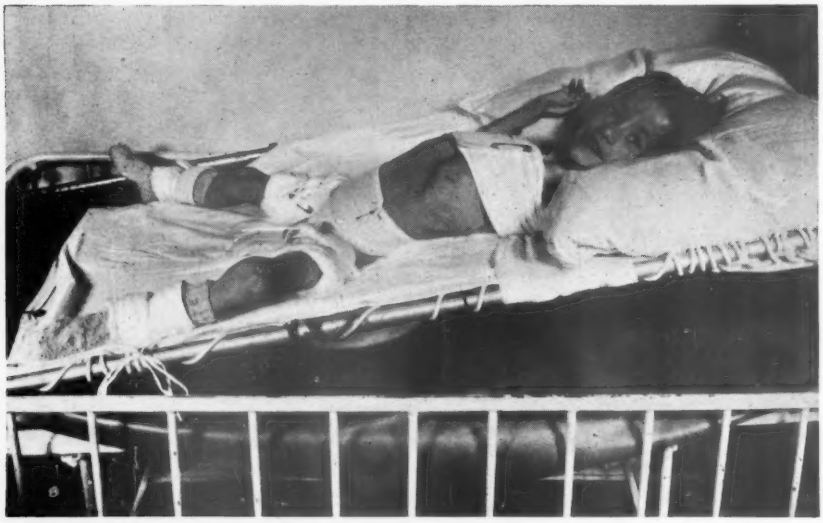

Plate I.

The child is placed so that the buttocks rest in the round hole. It is maintained in this position by a flannel binder. This consists of two double-thickness strips of flannel stitched together in the middle by two transverse, parallel lines of stitching (Fig. 2). The shorter strip (2 ft. 3 in. × 5 in.) is uppermost and the ends are pinned round the child. The

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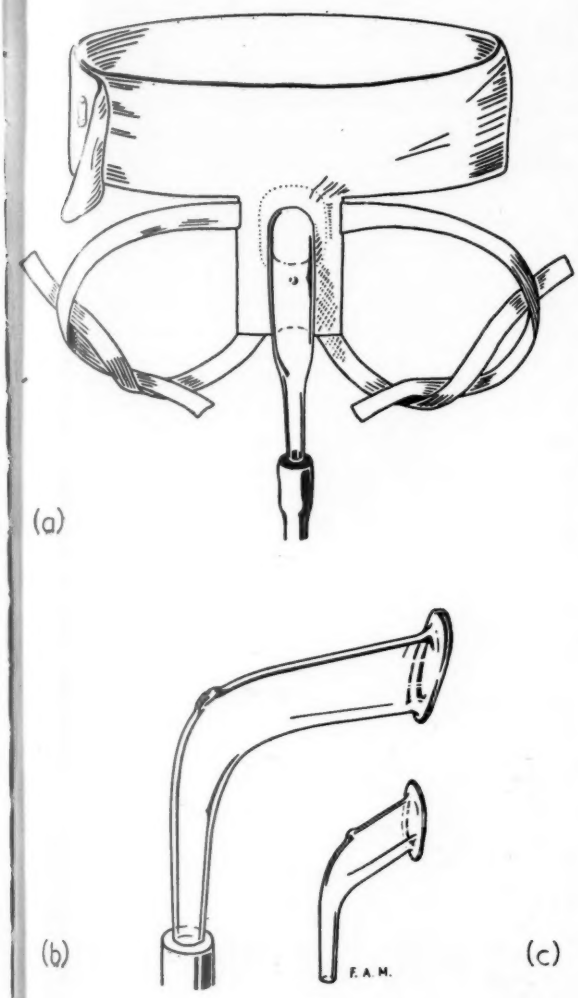

Fig. 2.

PLATE. I—Photograph showing a child lying in the metabolic bed.

FIG. 1.—Diagram showing the canvas frame in detail, the hole for the child's buttocks, and binders to hold the child to the frame.

FIG. 2a.—Flannel binder and attachment to which is affixed the urinal (Figs. 2b and 2c.)

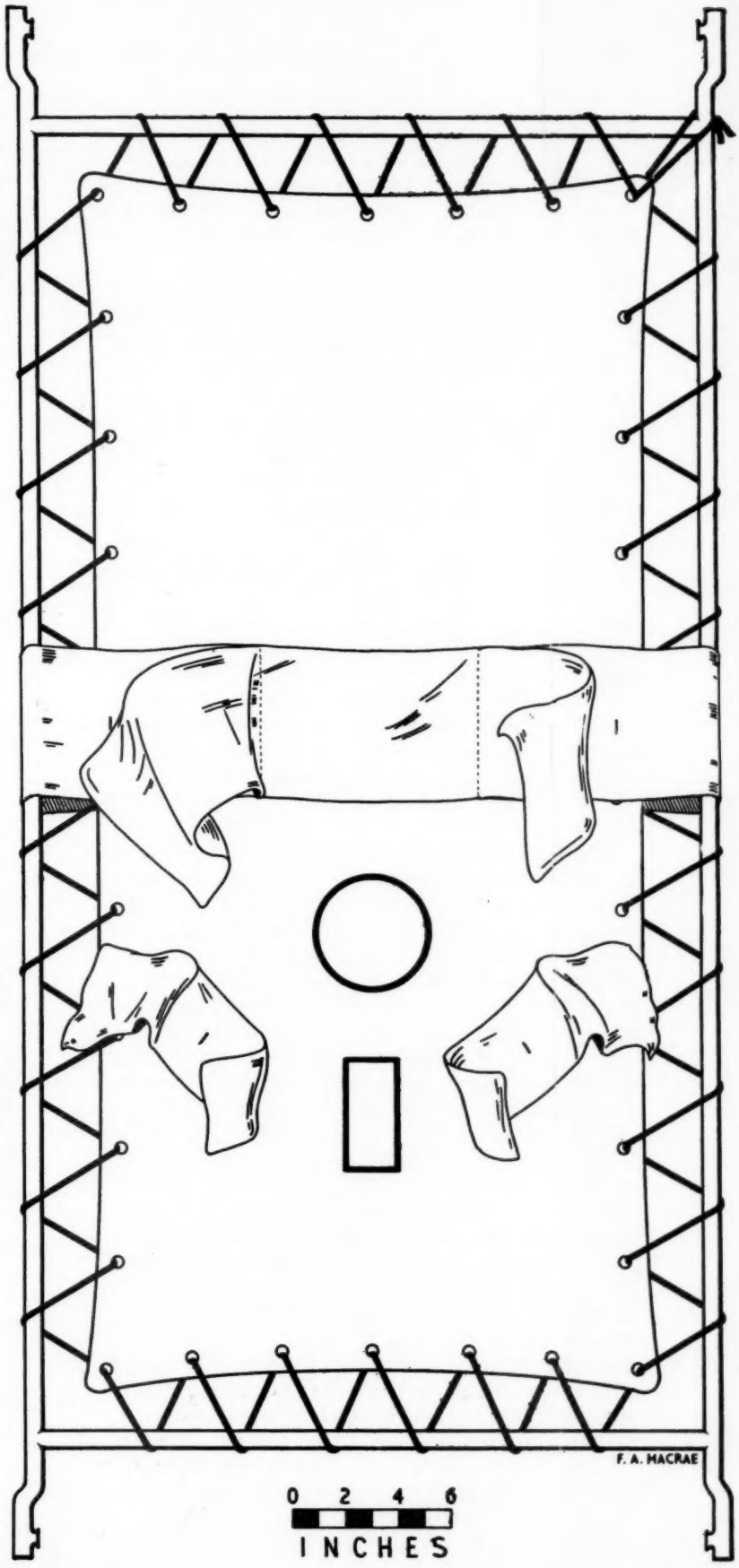

Fig. 1.

longer strip (5 ft. × 6½in.) is next to the canvas and the ends are folded over the sides of the frame at the appropriate level and pinned on the underside.

Two small binders are pinned on the canvas (from the underside) on either side of the hole and the ends pinned round the thighs so as to hold them in abduction. The leg below the knee can be free or, if necessary, may be fixed as in Plate I.

A glass urinal 8½ in. long and 1¼ in. diameter (Fig. 2b) is slipped over the penis, and held in place by a fourth, specially designed, binder (Fig. 2a). This consists of a strip of flannel 2 ft. × 4 in. which is pinned round the child's pelvis. It has in front a miniature ' apron ' with a hole in it exactly fitting the urinal below the flange. There are two narrow strips on either side of the ' apron ' which tie round each thigh.

An enamel bowl, or a bedpan, is placed underneath the buttocks to receive the faeces. The urinal is connected by rubber tubing to a bottle under the cot.

There are several disadvantages in this method, the greatest of which is the degree of immobilization involved. It does not seem to occasion any discomfort in itself, and the arms are free and, when permissible, the legs below the knee, yet as it may have to be used for days on end it is bound to become irksome to the patient. The skin is apt to become sore in some patients where the buttocks press against the edge of the hole, although this can usually be prevented by tight lashing of the canvas to the frame to prevent sagging; also the child cannot sit up.

No modification has yet been found to make the method suitable for girls (although we are still hoping to do this).

Apart from these objections the apparatus is entirely efficient, there being no leakage. The only risk of loss is during washing and weighing, which should be accomplished as rapidly as possible. A child of any age can be nursed on it up to that age at which such appliances are unnecessary. In some toddlers it has been found useful at night, when incontinence is more likely, even when it is not required by day.

For premature and marasmic infants, who should be nursed on their sides, with frequent changes of position, the metabolic bed is unsuitable, although Gordon, Levine, Wheatley, and Marples (1937), Levine, Gordon, and Marples (1941), and Levine, Dann, and Marples (1943) apparently used a modification of Hoag's apparatus for these patients. Schloss and Crawford (1911) devised a method in which the glass tube was held over the penis by adhesive tape stuck on to knitting wool which had been wound round the body. The faeces were collected in a rubber napkin and washed off with a known quantity of water. Coulson and Stewart (1946) fastened a rubber tube over the penis with adhesive tape. The objection to both of these methods is the adhesive tape, which rapidly damages a fragile skin, and fails to stick if it becomes damp. Thomson (1944) used rubber aural syringes held on with straps. Numerous attempts were made to use this method, especially as it was the only method encountered which could be used for girls, but no system of straps could be found which was tight enough to be efficient, and yet did not cause oedema and excoriation. For a study in premature infants

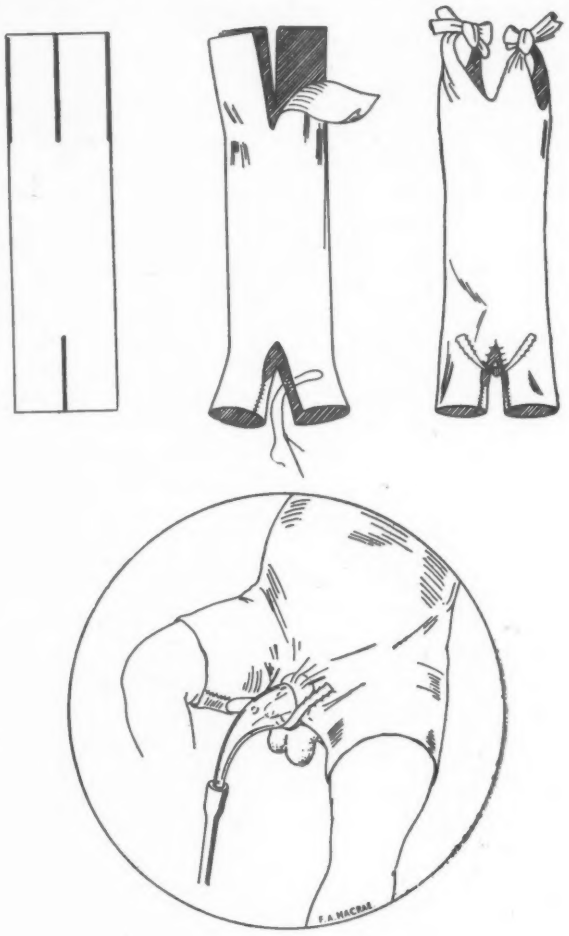

Fig. 3.

in which only the urine was required the following method was eventually devised.

The apparatus consists essentially of a pair of combinations, made out of plaster stockinette, to the front of which is stitched a piece of elastic. This holds a glass tube in position over the penis.

Apparatus for Marasmic and Premature Infants

A piece of plaster stockinette 15 in. long and 4 in. wide is cut down as shown in Fig. 3 (i.e. in two places at

the lower end and in four at the top, to make ' shoulder straps '). The cut edges on either side of the lower slit are sewn together for 1 in. upwards to form ' legs '. A piece of elastic 2 in. long and ¼ in. wide is sewn across the upper part of the slit in front at an angle to the midline, so that the free part in the middle is in a plane at right angles to the rest of the garment. It is as well to stitch round the rest of the hole which is to receive the tube, to give a firmer edge. The tube should be made as in Fig. 2c (considerably smaller, though similar to, that used for the metabolic bed). It is as well to have several sizes, ranging from 12 mm. to 16 mm. diameter. The hole in the ' dorsum ' of the tube is very important as it prevents the penis becoming oedematous.

The combinations should be put on first and drawn well up, and knotted or tacked on the shoulders. The slit should be extended upwards at the back, so that the chances of soiling are minimized. The tube is then slipped over the penis and into the hole above the elastic, which should grip the tube firmly below the flange. The lower end of the tube is connected by rubber tubing to a bottle under the cradle.

A triangle of gamgee is wrapped round the child in the usual way, and the point is not brought up between the legs but is left free.

It is important that the mattress should be sloped. This is done by means of a specially made board which slips into the cradle under the mattress and raises the head end. In addition, the head of the cradle is hung from a higher hook at the head end, and a lower at the foot.

The advantages of this method are: (1) The baby is not immobilized in any way. (2) There is nothing to harm the skin, or cause discomfort. (3) The glass urinal can be slipped on and off without removing the combinations, and therefore without having to undress the baby.

This apparatus has been used on premature infants for eight days in succession without loss of urine or trauma.

Recently it has been found that, when using this method on more active healthy full term infants, additional measures are necessary to prevent the baby kicking the tubing off. The simplest and most effective of these is a napkin, put on outside the combinations in the usual way, but with the two points brought up separately in front and pinned one on either side of the tube.

With these methods and modifications we have found it possible to make any collections required, so far, from boys.

Problems of Marking

There is great variation in the time taken for food to pass through the gut, in different individuals and also in the same individual on different occasions. It is therefore necessary, when assessing accurately the faeces relevant to a certain period, to mark the beginning and end of the period with some substance which when given orally will be recognizable in the faeces. The most widely used marker seems to be carmine, both in this country and in the United States. This has the advantage of being easily administered but it also has the great disadvantage of spreading within the gut, giving a very indefinite end-point and, in some cases, it apparently causes purgation.

Macy, Reynolds, and Souders (1939) have done an extensive investigation into the use and action of carmine. In a survey of healthy children it was given every fifth day for eight months. As it seemed at times to have a laxative effect, this was investigated. Barium meals containing carmine were given and serial x-ray films taken at intervals until the meal had been eliminated. A control series was done without the carmine in the same individuals. In the seven children investigated there seems to have been a remarkable uniformity of response. Although there was considerable ' hurry ' through the stomach and upper part of the gut, this was compensated for by a slower passage through the large intestine than the control meal. In every case the entire marker seems to have been excreted in the second defaecation after ingestion and they conclude that no laxative effect was demonstrated. This has not been our experience, as Table 1 will show. This illustrates the results after giving two drachms of liquor carminae (6%) to 25 children of varying ages with normal gastro-intestinal function. There is wide variation in response, and extensive ' spreading ' in some cases. In case 6 there was definite purgation, the first carmine stool appearing four hours after ingestion and being looser than normal. In the case which was slowest to respond, a further test was made, with a much more rapid result. As there was such a wide variation, it was thought worth while trying to establish where, in the gut, the variation occurred. For this purpose serial films were taken following barium meals (in water) in four normal children (Table 2). In all these the meal was in the colon in nine hours, although the time taken to eliminate the meal varied from 24 hours to six days. In view of this result it was thought probable that the whole meal could be recovered in 24 hours by giving a colonic washout.

Four children were given a barium meal and a film was taken 24 hours later. An enema was then given and another film taken immediately afterwards. In every case the second film showed that very nearly complete elimination had occurred. Compared with the carmine method, very much greater

TABLE 1

RESULTS AFTER GIVING LIQUOR CARMINAE (2 DR.) TO CHILDREN WITH NORMAL GASTRO-INTESTINAL FUNCTION

No.	Age	First Appearance of Carmine (in hours)	Other Appearances (in hours)	Final Appearance (in hours)
1	3/12	24		26¾
2	4/12	14½	20	
3	5/12	15		
4	9/12	14¼	17, 28, 45	48
5	1	13¾		19½
6	1	4½	16	40
7	1 2/12	11		
8	1 2/12	21	41½	43
9	1 4/12	17	41½	70
10	1 6/12	48½		
11	2	14	23	39
12	3	19		41½
13	3	41		
14	3½	18½		47
15	4	46½	63	69
16	4	15½		23
17	4	13	46½	60
18	5	42½	69	111¼
19	5½	15	47½	71½
20	7	17½		41
21	9	23		71
22	9	51		73
23	10	25		
24	10	19	110	163
25	11	120	140	166

accuracy could be obtained by this means. Unfortunately, there are two disadvantages: first, the increased discomfort and psychic trauma to the child, and secondly, the enormous amount of drying of the stool required when the colonic washings are included, and this must occur either at the beginning or the end of the metabolic period.

Until a better marker is devised, therefore, we are still using carmine.

TABLE 2

RESULTS OF SERIAL FILM SHOWING POSITION OF BARIUM MEAL AT INTERVALS AFTER INGESTION

No.	Age	Time Interval (Hours)						
		9	24	30	48	54	72	78
1	10	Round colon in rectum	Mostly in rectum	Same	Same			
2	6	Some in stomach ; rest in colon	Almost eliminated					
3	6	All in colon	Pelvic colon	Mostly pelvic colon	Same	Same	In rectum	Clear in 84 hrs.
4	7	In caecum	Pelvic colon	Same	Rectum	Rectum		Some in rectum at 98 hours. Eliminated at 6 days

Summary

A metabolic bed is described, and methods of collecting urine quantitatively from premature and full-term infants.

The advantages and disadvantages of each method are discussed.

An investigation into the efficiency of carmine used as a marker is described.

Acknowledgments and thanks are due to Professor Moncrieff who instigated the work on metabolic apparatus, and to Dr. W. W. Payne who suggested and directed the work on markers; to the Belle Vue Hospital, New York, for the basic idea of the metabolic bed; also to the nursing staff concerned, especially that of the Premature Baby Unit at the Postgraduate Hospital, Hammersmith, for their co-operation and gallant perseverance; and to Mr. D. Martin (Hospital for Sick Children) for the photograph.

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A METHOD OF COLLECTING TOTAL EXCRETA IN INFANTS

BY

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(RECEIVED FOR PUBLICATION OCTOBER 1, 1949)

It has recently been stated (Sheldon, 1949) that none of the methods described for conducting ' balance ' experiments on incontinent children have as yet proved satisfactory. We are prompted, therefore, to describe the method which we have employed for some time in this hospital.

A special type of bed is used, designed on the principle of the metabolic cage for animal experiments. It consists of a wooden cot with solid sides and ends, with a removable grid-mattress constructed of interlaced rubber tubing stretched in a wooden frame. Below the mattress is a funnel-shaped zinc collecting chamber, the outlet pipe of which can be inserted into a collecting vessel. The bed was made in the hospital workshop (Figs. 1, 2, and 3).

The bed is used in a side room where the temperature is kept at 90° F., and the child is unclothed except for a short vest. The head pillow is mackintosh-covered (in case of vomiting) and lies directly on the rubber grid. On this, and under the child, is a mackintosh sheet which stops at the child's mid-lumbar region. If required, a harness can be worn, the ties being passed through holes in the sides of the bed and fixed to brackets on the outside. Practically all the excreta automatically pass into the bottle underneath the bed, and any that adhere to the grid or collecting chamber can be easily washed into the receiving bottle with distilled water, without much disturbing the child.

Separate urine specimens were collected by indwelling catheterization in the female and in the male by connecting a rubber tube to the penis by a finger stall. These methods were found more satisfactory for the age group which we studied than the method described by Thomson (1944). The separation of specimens in the female was limited to periods of 24 hours.

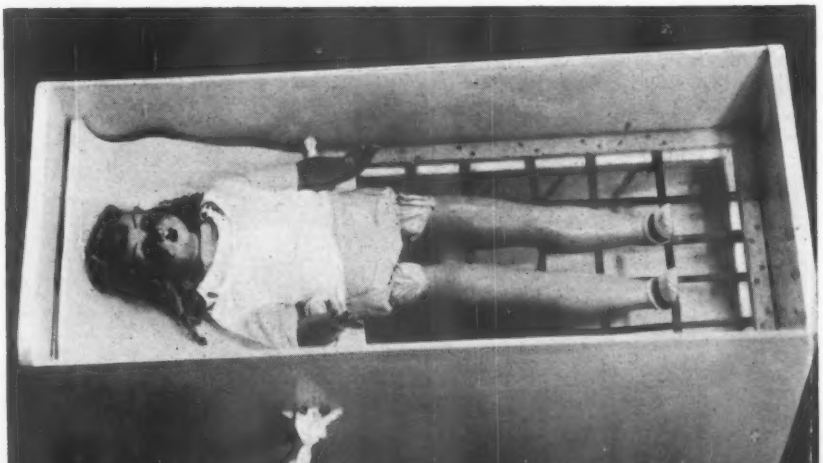

FIG. 1.—Photograph showing position of patient in metabolic bed.

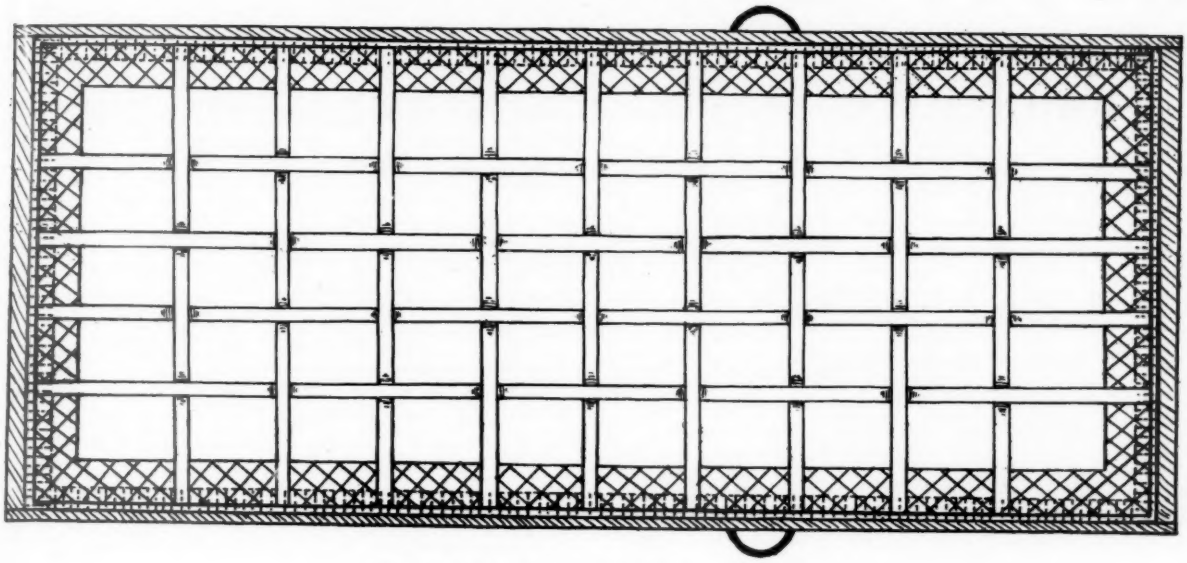

Fig. 2. Diagram showing grid-mattress.

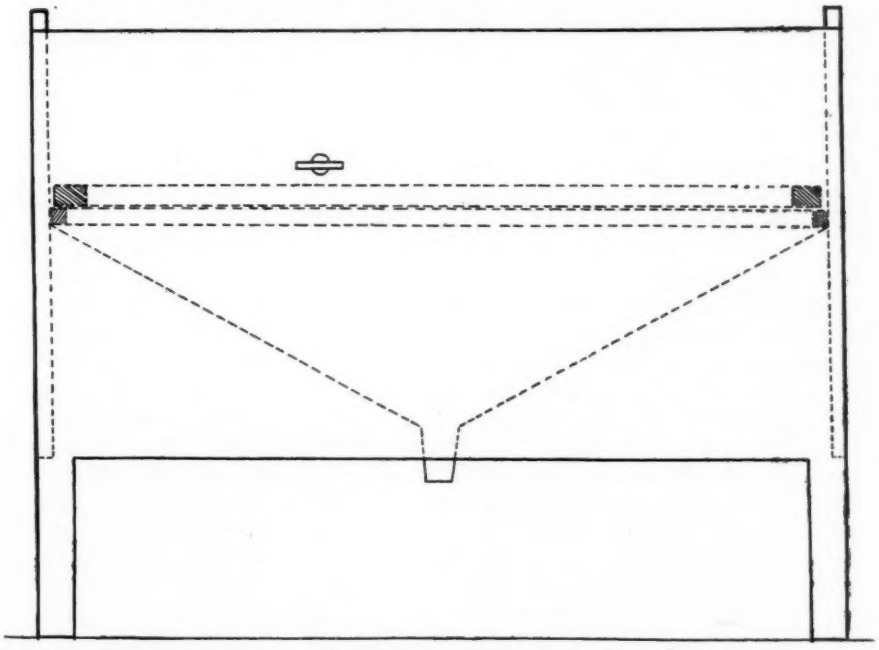

Fig. 3. Side view of the cradle.

There have been no nursing difficulties. The child becomes accustomed to the bed within 24 to 48 hours, and gains in weight in a normal way while in it. It might appear that there would be a danger of the legs becoming entangled in the mesh of the mattress, and this may happen within the first 24 hours, but the child soon acquires the habit of lying with his legs drawn up or of hooking his toes round one of the pieces of rubber tubing. He remains remarkably contented and sleeps normally. The child does not often soil himself, and when he is old enough to sit up no difficulties have been encountered.

We have used the bed with children between the ages of three months and a year. They have remained in it for periods up to seven days without any suggestion of bedsores, and rather surprisingly, there were no unpleasant odours provided the receiving vessel was changed daily.

We have pleasure in thanking Dr. James Thomson for clinical facilities and Professor Lendrum for help with the presentation.

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GONOCOCCAL VULVOVAGINITIS IN INFANTS AND CHILDREN: A STUDY OF 240 CASES

BY

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Gonorrhoea in women often produces minor symptoms. This explains the comparative infrequency of symptomatic gonorrhoea of the lower genital tract in out-patient clinics. Gonococcal infection of infants and children, on the other hand, at once attracts attention. Hence the reason why the incidence of vulvovaginitis infantum appears to be comparatively high. Nelson (1932) found the incidence of gonorrhoeal vulvovaginitis to be 11·8% and Mukherjee (1940) 11%. In a series of 2,464 cases in the female, diagnosed by bacteriological methods during 1933-46, we came across 240 cases of gonorrhoeal vulvovaginitis, a frequency of 9·7%.

Not all cases of vulvovaginitis are caused by gonorrhoea. Foreign bodies, non-specific infections caused by unhygienic conditions, threadworms, exanthematous fevers, monilia, and diphtheria account for a fair number. Fessler (1930) found gonorrhoea in two out of 25 cases, and Clauberg (1930) failed to cultivate the gonococcus from 70 children examined for the condition. Ruys (1935) found gonococci in 57 out of 292 children. During the period under review the total number of vulvovaginitis cases was 438, of which 240 (55%) were diagnosed as gonorrhoeal. This may appear to be high and is probably so, for most patients with simple catarrhal vaginitis do not report to hospitals for investigation and treatment. It may be of interest to compare the relative frequency of gonorrhoea with the other aetiological conditions causing vulvovaginitis in children (Table 1).

TABLE 1

COMPARISON OF AETIOLOGICAL CONDITIONS CAUSING VULVOVAGINITIS

Nature of Infection	No. of Cases	Percentage
Foreign bodies	26	5·9
Non-specific infections ..	156	35·6
Diphtheria	2	0·5
Exanthemata	2	0·5
Mycotic	12	2·7
Gonococcal	240	54·9
Total	438	100·1

The incidence of gonococcal infection in any study of vulvovaginitis is dependent on the means employed for the detection of gonococci. The unreliability of smear examination alone has been shown by several observers (Clauberg, 1930; Ruys, 1935). This is because of the presence of Gram-negative cocci, which are often arranged in pairs, in the normal vagina. Greenhill (1945) suggested that to identify gonococci one must discover more than ten typical organisms intracellularly in the same slide, and two or more within the same cell. By a similar method it has been possible to eliminate no fewer than 31 cases in the present series. Subsequently culture and the progress of the patient demonstrated the usefulness of this simple suggestion. There is another difficulty in chronic or inadequately treated cases. In these the vaginal exudate is scanty, and leucocytes are fewer and more disintegrated. In these cases, even if Gram-negative diplococci are found in the smear they are frequently extracellular. A negative report in these cases does not completely rule out the possibility of a true gonococcal infection.

Cultural results are more reliable, provided the exudate is fresh and inoculated immediately. Clauberg (1930) was one of the earlier observers to emphasize the value of routine culture. Mascall (1933) also found a higher incidence of positive results on cultural examination. Cohn, Steer, and Adler (1941) showed from the results of 1,070 examinations that cultures were positive in 98·9% of cases, whereas positive results on smear examination alone obtained in 67·1%. These authors value cultural methods not only in diagnosis but also in follow-up treatment. In our series culture was not possible

in all cases, but the relative value of culture and smear examinations is tabled below (Table 2).

TABLE 2
COMPARISON OF CULTURE AND SMEAR EXAMINATIONS

Method of Examination	No. of Cases	Percentage
Culture + smear + ..	98	40·8
Culture + smear − ..	52	21·6
Culture − smear + ..	9	3·8
Smear (only)	81	33·8
Total	240	100

It would appear that culture was positive in 62·5% of all cases. Excluding the cases where cultural facilities were not available, positive culture was obtained in 94·3%, while smear examination was positive in only 61·0%. As a general rule more culture-positive cases are seen in chronic conditions. Incidentally, this increases the value of culture in assessing the criteria of 'cure.'

Mascall (1933) believed that the largest number of positive results could be obtained with the complement fixation reaction. His observation on cases at the London County Council clinic at Whitechapel showed 79·6% positive results with the complement fixation test, 66·8% positive results on culture, but only 45·4% by smear examination.

Age Incidence

The principal reason for the widespread infection of the vulva and vagina in the young is the absence of the normal protective acid vaginal secretion in these subjects. This also explains the rarity of gonococcal vulvovaginitis in very young infants. The youngest patient with gonorrhoeal infection of the vulva and vagina was reported by Wattie (quoted by Cruickshank and Sharman, 1934) in an infant of 5 months old. Wynkoop and Boggs (1926) in a study of 500 infants during the first two weeks after birth failed to detect a single case of vulvovaginitis of gonorrhoeal origin. In a similar study of 36 infants during the first 15 days after birth where the mothers had gonococcus in the lower genital tract before, and/or during labour, no case of gonococcal vulvovaginitis was detected. It is of interest to note, however, that 24 of them developed the infection between two and a half and 13 months after birth.

By far the largest number of cases are usually found in early childhood. Nelson (1932) found 44·9% of cases between 5 and 9 years of age. Mukherjee (1940) found the highest incidence in Bengal to be 45·6% in girls from 3 to 5 years of age. The distribution of age of the cases in the present series was as follows (Table 3).

TABLE 3
AGE DISTRIBUTION OF PRESENT SERIES

Age	No. of Cases	Percentage
Under 6 months	4	1·6
6 months to 1 year ..	24	10·0
3 years to 5 years ..	114	47·5
5 years to 7 years ..	30	13·5
7 years to 9 years ..	19	7·9
Over 9 years	8	3·3

The youngest patient in this series was a girl of 2½ months and the oldest one was one of 11 years. The highest age incidence in this group was 3 to 5 years, as in a previous group which I reported in 1940.

Source of Infection

To trace the source of infection is difficult but important from the public health point of view. Boarding schools, dormitories, or infected bath tubs may account for an occasional case in India, or the sudden outbreak of an epidemic in an institution, but certainly in most cases these factors play a negligible role. Rape or superstitious beliefs account for a small number. In the majority, where the source can be traced, either a member of the family or a servant plays the rôle of carrier. In the present series the source of infection was apparently traceable in only 145 cases (60·4%) although 186 parents and immediate contacts were examined. Of these 81 (43·09%) harboured gonococci. In 86 cases the servant was examined and gonococci were discovered in 70. In 11 cases both the attendants and immediate family contacts harboured the infection. In five cases the infection was traceable to other children in the family, or to playmates.

Clinical Features

The incubation period could not be properly ascertained owing to difficulty in obtaining the history of the time of exposure. An attempt was, however, made to estimate it where the source of infection was detectable, but the result is not very satisfactory (Table 4).

The symptom which attracts attention is a discharge. This in the early stages is sero-purulent, but within 48 to 72 hours becomes frankly purulent. If cleanliness is not maintained the odour of decomposing pus is noticeable. The discharge is not as a rule sanguineous, but in three

TABLE 4
ANALYSIS OF INCUBATION TIMES

Incubation Period	No. of Cases	Percentage
Less than 24 hours ..	10	12·8
25–48 hours	22	28·2
49–72 hours	28	35·9
73–96 hours	18	23·1

hyperacute cases a sanguineous discharge was noticed. Incidentally it may be mentioned that a sero-sanguineous or sanguino-purulent vaginal discharge in infants has been found in all cases of foreign body vaginitis. The discharge of vulvovaginitis is of a remarkably irritating nature and in a few days (less than four days in 86% cases) signs of irritation of the vulva, groin, perineum, and peri-anal regions appear.

Dysuria was present in 194 cases (80·8%). Belladonna usually relieves this dysuria to a great extent. A considerable part of the complaint is probably due to urinary tract infection and spasm.

The first symptom observed in the patient was: (1) Discharge, 187 cases (77·9%); (2) vulval irritation, 47 cases (19·6%); (3) dysuria, 6 cases (2·5%).

Examination usually shows severe inflammation of the vulva. The labia are swollen, tender, and excoriated. The vestibule is bathed in pus, and is angry and congested. The urethral orifice is swollen and pouting, but infection of Skene's glands was never noticed, nor was Bartholin's gland affected. In one case the infection was so severe, and lack of cleanliness so pronounced, that noma of the vulva had developed before relief was sought. The extent of ulceration of the vulva is usually proportional to the infection. In such fulminating cases the nature of the basic infection is often missed, especially on culture, as secondary organisms grow exuberantly. This happened in no less than 23 (9·6%) of our cases. In such a predicament microscopical examination of a carefully prepared slide exposes the possibility of the nature of the underlying infection. It must be said, however, that as the secondary infection comes under control, culturing gonococcus from the vulvovaginal secretion becomes more easy.

Inspection of the vagina when the infection is acute is not only almost impossible but is also dangerous, for an acute flaring up of the infection is the usual consequence. Nevertheless, after washing the vulva under a gentle stream of normal saline, the degree of severity of the infection can be judged from the amount and nature of the vaginal discharge. Gentle milking of the vagina with the little finger introduced into the rectum is all that is necessary. When the active infection is under control the state of the vaginal mucous membrane can be inspected with a Kelly speculum or an electric cystoscope. A small dose of luminal about one and a half hours before instrumentation helps to allay nervousness. The usual finding is a congested swollen mucous membrane bathed in a purulent exudate. In 79 cases (32·9%) superficial ulcerations were noticed. Evidence of infection is as a rule more marked in the lower half of the vagina than in the upper and on the posterior wall than on the anterior. The cervix often shares the vaginal infection (30%).

The spread of infection to the upper genital passages is rare, owing to the protective barrier of the cervix. Nevertheless exploration of the pelvis during rectal examination is sometimes rewarded. In our series only four children developed evidence of peritoneal involvement (1·68%). In a similar study by Schauffler (1940) of 266 infants and children with frank vaginal infections nine presented symptoms of pelvic involvement. Lees (1928) gives the frequency as no less than 5·5%.

In our series rectal symptoms were present in 14 cases or 5·8%. Rectal infection forms a hidden focus from which re-infection and relapse are frequent. Fraser (1925), Williams (1933), and Martin (1935) were some of the earlier observers to direct attention to this possibility. Fraser found rectal infection in 59 out of his 63 cases. Ruys (1935) observed it in all cases in his series. In an earlier report (1940) I found rectal infection in 82%. Material from the rectum was examined, by smear and culture, in 170 cases (70·8%) of this series. Culture was positive in 168 cases (98·8%); smear examination was positive in 124 cases (72·9%).

Collection of Material for Diagnosis

It is a mistake to collect the material from the vulva because extraneous organisms are so abundant in this region. The following method has been found useful.

Method. The vulva is washed under a gentle stream of sterile warm normal saline. A narrow, but strong glass pipette is then introduced into the vagina and a drop of exudate is collected from this region. Sometimes the pus is too thick for the calibre of the pipette. In these cases about ½ to 1 ml. of sterile saline may be introduced before the material is collected. Inoculation in the culture medium on to hydrocele or ascitic fluid agar in petri plates is made immediately. After inoculation a smear preparation may be made with the remainder of the exudate and stained by Gram's method.

Examination of the rectal specimen formed a routine, except for the first 70 cases studied. The material was

collected with a strong wire loop from half an inch inside the anus after holding the child in an exaggerated lithotomy position and stretching the anal skin. Inoculation was done immediately. For a rectal smear the discharge collected on the loop may have to be mixed with a drop of sterile saline on a slide.

Complications

Complications are uncommon in gonococcal vulvovaginitis. Contrary to the usual expectation ophthalmia develops only rarely. I have found (1940) the incidence to vary from 1 to 5%. In the present series gonococcal ophthalmia developed in 18 cases (7·5%). It is, however, interesting to note that whereas in 14 cases the ocular infection followed the vulvovaginal lesion, in two the infection of the eye was primary. In the remaining two cases the parents declared the infection to be about synchronous. It is also interesting to note that in all these instances the mother was a carrier of infection.

Arthritis was also found to be uncommon. The joint most commonly affected was the knee. The onset is sudden and not infrequently it is confused with osteomyelitis of the lower end of the femur. The joint is swollen and a cutaneous flush may be present; pyrexia varies between 100·6 and 103° F. The tenderness is, however, limited to the joint, the bone ends being free. The lesion is of the monoarticular type. Williams (1926) considers this complication to be very frequent. In our series, however, it was encountered in only seven cases (2·9%). The knee was the seat of lesion in all, though in two instances the ankle was subsequently affected. Although the joint fluid was examined on nine occasions, gonococci were cultured only once. In no case did ankylosis or limitation of movement result.

King, Mascall, and Price (1936) drew attention to associated infection with trichomonas and stated that it interfered with the demonstration of gonococci. I can corroborate this statement. In the present series no less than 36 (15%) patients harboured trichomonas, besides eight, in which infection was suspected but could not be confirmed until about three weeks after the first observation, a total incidence of 17·5%. It has now been our practice to examine a hanging drop preparation of the vaginal discharge (diluted with saline) on three successive days before associated trichomonas infection is ruled out. In this connexion the case reported by Karnaky (1936) is interesting. Trichomonas infection makes gonococcal infection more resistant to treatment, besides causing the irritant vaginal discharge to persist even after the disappearance of gonococci. If the trichomonas infection is missed initially it is usually detected later when leucorrhoea becomes persistent, but early detection shortens the course of treatment considerably. It has not been possible to detect the source of this obstinate secondary invader. The vaginal mucous membrane of infants is very susceptible to trichomonas infection. The mutation of *Trichomonas intestinalis* into *T. vaginalis in vivo* has been suspected but has not been actively proved. In 16 patients of the series intestinal trichomonas were detected in the faeces, but almost all these patients belonged to a class of society where personal hygiene was minimal. Of 86 'better class' patients only one showed this secondary infection.

Associated luetic infection cannot strictly be regarded as a complication, but it is important. Out of 198 cases in this series where a routine Wassermann test was done, 46 (23·2%) were positive. This cannot be accepted as it stands because of the possibility of inherited syphilis. If 37 cases, where the parents also had positive blood tests, are excluded, the incidence of associated syphilitic infection appears to be only 4·5% (nine cases). It may be pointed out that in eight out of these nine cases a history of rape was either present or suspected. It appears that the presence of an associated syphilitic infection, if inherited syphilis is excluded, indicates a criminal assault.

Treatment

For comparative study the results obtained in all cases are presented in relation to the form of treatment.

Orthodox Local Treatment. The total number of patients treated was 20. The treatment consisted of hip bath, vaginal irrigation, and instillation of silver nitrate or mercurochrome solutions.

Straightforward uneventful recovery was an exception; relapses were frequent, the course of therapy prolonged, and taxing to the patience of the parents and the medical attendant. The average duration of treatment was 12 weeks, while the minimum was 10 weeks and the maximum 26. If it is considered that all patients with relapse came back for treatment (an expectation which is extremely improbable) its incidence appears to be 20·0% (four cases). It was also noted that the relapses were more refractory to local treatment alone than the primary infection. The results of local therapy may, therefore, be considered unsatisfactory.

Sex Hormone Therapy. The total number of cases treated with sex hormones was 102. In 70 of these oestrogen therapy was combined with local antiseptic treatment. In the remaining 32 oestrogens

alone were employed locally. Lewis (1933) observed that female sex hormones in children produced proliferation of vaginal epithelium and the clearing up of the vaginal infection. But the effect of oestrogens is not confined to the vagina. Witherspoon (1935) suggested that prolonged use of oestrogens might inhibit the pituitary and bring about secondary atrophic changes in the ovaries. It has, however, not been conclusively shown that such changes affect infants and children equally. Of the 102 patients of this series treated with oestrogens 31 have been followed up to the age of puberty and thereafter. The age of the menarche in this group may be tabulated here with advantage (Table 5).

TABLE 5

AGE OF MENARCHE OF CASES TREATED WITH OESTROGENS

Age of Menarche (years)	No. of Cases	Percentage	Normal Controls
11–12	8	25·9	38
12–13	12	38·4	29
13–14	8	25·9	21
14–15	3	9·7	9
15–16	–	–	3
Total	31	99·9	100

Table 5 shows that there is a tendency for a delayed menarche in the group of children treated with oestrogenic hormones in infancy, but it must be admitted that the number of cases is so small that the difference may be more apparent than real. In any case the advantages of oestrogen therapy in vulvovaginitis far outweigh the supposed fear of pituitary inhibition and ovarian atrophy. No difference in results has been observed between oral and parenteral treatments if the dosage has been adequate. Often both these means of administration have been combined.

NATURAL OESTROGENS. The preparations employed were ' progynon B oleosum,' ' ovocyclin P,' and ' menformon.' The number of cases so treated was 48 (64·4%, i.e. 20·0% of all cases). The dose employed was 1 mg. (10,000 I.U.). Except in the case of very small infants (up to 3 years) this was supplemented with a daily dose of 0·3 mg. (3,000 I.U.) of oestrogen dragees orally in divided doses. The course of treatment was checked by frequent vaginal smear and culture and estimation of the vaginal acidity. Improvement was invariably attended with a fall in the vaginal *p*H, often to the extent of 3·5 to 4. This substantiates the observation made by Karnaky (1936) who recorded recovery in every case in a series of 140 when the *p*H was brought down to 3 to 3·5. He used dextrose-acid tablets which were inserted into the vagina. Oestrogens produce a similar effect in an indirect manner.

SYNTHETIC OESTROGENS. The preparation used was diethyl-stilboestrol. The number of cases treated in this group was 22 (35·6%, i.e. 9·1% of all cases). All patients had oral medication in doses of 1 mg. daily. Infants under 2 years of age were given 0·5 mg. It may be mentioned here that except in two cases no toxic symptoms were noted. These were manifested as vomiting and irritability which were relieved with small doses of calcium and sodium bicarbonate.

In both these groups the local treatment consisted of cleaning the vulva and vagina with 0·75% lactic acid and instillation of 2% mercurochrome in the vagina.

It was observed that with oestrogens (both synthetic and natural) considerable improvement occurred in about two and a half to three weeks, though for complete recovery the treatment had to be continued for five to six weeks, or longer. It must be mentioned, however, that examination for gonococci became negative on smear 10-14 days earlier than on culture. If reliance is placed on smear examination alone, the patient may still remain a carrier and as such, a source of danger.

Even after the vulva and vagina were free from infection rectal infection persisted, and acted as a focus of reinfection for the vagina, with subsequent relapse of the condition. In fact the incidence of relapses after oestrogen therapy was 15·7%. It was, therefore, considered necessary to institute treatment for the rectal condition while oestrogens were being administered for the vulvovaginal lesion, for in the absence of rectal infection relapse of vulvovaginitis never occurred after oestrogen treatment. The simplest remedy for the rectal infection was found to be 5% ' argyrol ' suppositories. One of these is inserted into the rectum at bedtime and retained.

The change in vaginal acidity was noted as early as eight days after the beginning of treatment. Irrespective of what the initial *p*H value was (the highest recorded was 9·8), by this time a distinct though slight acid reaction was noted. A steady increase in acidity continued until about the end of the third week when a *p*H of 4·5 to 4·8 was the usual finding. By about the beginning of the fifth week the peak was reached and the level maintained for about a week after the treatment was over. The reaction returned near to neutrality by about the seventeenth day after the suspension of treatment. The highest acidity which was obtained in

the present series of cases was *p*H 3·2. In spite of full courses of oestrogens the *p*H did not fall below 5·3 in four cases. In these patients residual infection persisted in the vagina though the rectal infection was under control with 'argyrol' suppositories. Lactic acid jelly (1%) was instilled into the vagina three times a day and complete recovery followed.

Comparative refractoriness of the vaginal acidity was noted in 17 patients in none of whom did the *p*H fall below 6·4 after three weeks' treatment. Heavy infection with *Trichomonas vaginalis* was found in all of them. When this infection was controlled the normal curve of the vaginal acidity was regained.

The change in the vaginal smear was found to be more gradual than that of the reaction. Polymorphonuclear cells persisted until the disappearance of the infection, although partially keratinized epithelial cells appeared in the smear within two weeks of the beginning of treatment. A real 'oestrus smear' was not obtained till the vagina was free from infection.

The average duration of treatment in this series was 6·0 weeks (Table 6).

TABLE 6
AVERAGE DURATION OF TREATMENT

No. of Weeks	No. of Cases	Percentage
4	17	24·3
5	18	25·7
6	12	17·1
7	9	12·8
8	2	2·9
9	4	5·7
10	4	5·7
11-12	4	5·7

In eight (11·4%) cases of this series, although marked relief of symptoms was obtained, the vaginal secretion was not free from gonococci and the *p*H did not fall below 6·4. Cultures showed infection with staphylococci, which produce alkaline exudates. These patients were subsequently treated with sulphonamides or/and penicillin and cured.

The criterion of cure was three consecutive negative reports on culture and smear examination, the last one after a provocative painting of the vagina with 1% silver nitrate solution. In 13 cases recurrence was noted within three to four weeks of recovery. The possibility of reinfection could be definitely eliminated in 11 patients. The incidence of relapse in this series may therefore be taken as 15·7% and the corrected recovery rate as 72·9%.

An inquiry was made into the difference in results obtained with natural and synthetic oestrogens (Table 7). It appeared that the synthetic product was slightly superior to oestradiol derivatives in its effects, besides being cheaper and more easily administered. Its toxic effects were not found to be marked in infants, and when present they were easily controlled.

Oestrogen Vaginal Suppositories. Thirty-two cases were treated with oestrogen vaginal suppositories. The preparations employed were 'kolpon' (organon) and stilboestrol jelly (10 mg. per g. tragacanth-glycerine jelly). Preliminary cleansing of the vulva and vagina with 0·75% lactic acid lotion was employed in all cases. No antiseptics were used, but the treatment of the rectal infection was not omitted. Results were found to compare favourably with oral and parenteral medication. The average course of treatment necessary was 5·0 weeks (Table 8). More than half the total number of cases needed only three to four weeks' treatment for complete recovery. By the tenth day considerable subjective improvement was often noted, while towards the beginning of the third week the vaginal discharge was scanty and seromucoid in nature in 29 cases (90·6%) of the series. A *p*H of 4·6 to 4·0 was usual about the middle of the third week. As with parenteral oestrogen therapy the initial change from alkaline to acid reaction took place in about eight to ten days, but once the acidity was established the fall in *p*H was

TABLE 7
COMPARISON OF RESULTS OBTAINED FOR NATURAL AND SYNTHETIC OESTROGENS

	No. of Cases	Course of Treatment			Cure	Relapse	Failure
		Maximum	Minimum	Average			
Natural oestrogens ..	48	12	5·5	6·6	38 (70·8%)	8 (16·6%)	6 (12·5%)
Synthetic oestrogens ..	22	10·5	4·0	4·7	17 (77·3%)	3 (13·6%)	2 (9·0%)

TABLE 8

DURATION OF TREATMENT WITH OESTROGEN VAGINAL SUPPOSITORIES

No. of Weeks	No. of Cases	Percentage
3	8	25·0
4	9	28·1
5	5	15·6
6	3	9·4
7	2	6·2
8	2	6·2
9	2	6·2
10	1	3·1

more or less steady and rapid. The rate of improvement was proportionate to the rate of attainment of this acid peak.

The treatment was without effect in three cases or 9·4%. The maximum vaginal acidity which was obtained in these cases was *p*H 5·2. Local treatment was continued for 12 weeks after which parenteral natural oestrogen therapy was employed for a further period of six weeks without any impression on the disease. Treatment with sulphonamides and penicillin subsequently cured these patients.

Permanent recovery was obtained in 26 cases or 81·1%. This is undoubtedly much less than the 98% cure reported by Te Linde (1938). Relapse occurred in three cases or 9·4%. The interval between apparent recovery and relapse was two to three weeks, which is shorter than after general oestrogen treatment. In these cases also the persistence of rectal infection appeared to be the cause of recurrence of symptoms.

UNTOWARD SYMPTOMS OF OESTROGEN THERAPY. Considering the dosage of oestrogens the incidence of untoward symptoms was negligible. They were not serious enough to call for withdrawal of the drug. In our series of 102 cases treated with oestrogens enlargement of the breasts was noted in 11 (10·8%). Of these, in eight cases the mammary changes were slight and just noticeable. In two cases where oestrogen injections were continued for over ten weeks the appearance of the mammary glands simulated that which is normally noticeable at or about puberty. In one case there was secretion, and pigmentary change was marked, though the hypertrophy was only moderate. Oestrogenic response of the breasts was more marked in the group treated with oral or parenteral oestrogens. Of the 72 cases subjected to general oestrogen therapy the breast changes were seen in nine or 12·5%, whereas these changes were noticeable in only two cases or 6·2% among the locally treated group. It was also observed that mammary hyperplasia was more likely to develop in the higher age group children than in infants. Eight out of the 11 cases (72·8%) with noticeable changes in the breast were above the age of 8 years, and two were in the 6 to 7-years-old group. Only one case below the age of 3 years showed this change and it was only slight. The two cases where the change was marked were both over 9 years of age. In all cases, however, retrogressive changes set in within ten days of the cessation of the treatment except in the two cases where the hypertrophy was excessive, and persisted to some extent until puberty. Reversion to normal occurred in less than four weeks.

Vaginal bleeding is another untoward sequel. Though it is of no grave consequence it often causes anxiety. Schauffler (1947) noticed it in only two cases in his series. In our series of 102 cases vaginal bleeding occurred in only seven (6·9%). With the exception of one, where the bleeding appeared during the course of treatment, in all the haemorrhage was of the nature of oestrogen withdrawal bleeding and started six to eight days after the completion of treatment. In none was the haemorrhage excessive and it stopped spontaneously in four to seven days' time. In one case (aged 9 years 7 months) the bleeding was accompanied by cramp-like pain in the lower abdomen. All cases of vaginal bleeding belonged to the group of cases treated with parenteral and oral oestrogens. Here also, as in the preceding instance, susceptibility to vaginal bleeding appeared to increase with increase in age. Only one out of the seven cases was below the age of 7 years, four cases were over 9 years of age, and two between 8 and 9 years. There appeared to be some relation between vaginal bleeding and mammary congestion and hypertrophy, for all the seven cases in which vaginal bleeding occurred showed breast changes.

A sparse growth of fine pubic and axillary hair was noticed in four cases (3·9%), in all of which the treatment was continued for ten weeks or more. Two of these patients were over 9 years old, one just over 7, and another just under 5 years of age. In all cases spontaneous retrogression occurred in less than six weeks.

Sulphonamide Therapy

The advent of sulphonamides induced high hopes of success in the treatment of vulvovaginitis. This optimism has not been wholly rewarded. Hoffman, Schneider, Blatt, and Herrold (1938) reported cure in 75% of cases after one of two courses of sulphanilamide. Brown (1939) obtained a similar recovery rate, although she succeeded in curing 81·4% with a four-day course of sulphapyridine.

Lewis (1940) obtained a 90% recovery rate with this drug. Cohn, Steer, and Adler (1941) succeeded in obtaining negative cultures in all cases with sulphapyridine. Adair and Hac (1942) made a comparative study of the value of the different sulphonamide products and found that the rate of cure with sulphanilamide was 76%, with sulphapyridine 86%, with sulphathiazole 93%, and with sulphadiazine 96%.

In our series of 240 cases sulphonamides were administered to 83 patients. Sulphanilamide and sulphapyridine were used in only 10 and 13 cases respectively. Toxic symptoms appeared frequently when these drugs were used. These 23 cases have not been included in the series under review. Of the 83 patients considered here, 46 were treated with sulphathiazole and 37 with sulphadiazine. No special local treatment was given except cleansing and hip bath.

The dosage employed was 32 mg. per lb. body weight. With sulphadiazine in the case of feeble children a slightly smaller dose (24 mg. per lb. body weight) was employed. The initial dose was double the calculated dose. The maintenance dose was repeated every four hours. In the case of children weighing more than 15 to 16 lb. the dosage was so regulated that the total intake did not exceed 2 g. a day, and 16 g. during the whole course. This was found to be the maximum safe limit.

Within 48 hours of the administration of sulphathiazole or sulphadiazine subjective improvement was noted. The majority of cases showed a negative smear and culture in less than 96 hours, but it was found unwise to withhold the drug at the first negative reading, for in a number of such cases recurrence occurred. The minimum course of treatment compatible with recovery was found to be one of four days, and the maximum eight days, while the average duration of treatment was 5·9 days. The distribution was as follows:

4 days	..	11 cases (13·2%)
5 days	..	29 cases (34·9%)
6 days	..	32 cases (38%)
7 days	..	7 cases (8·4%)
8 days	..	4 cases (4·8%)

Lewis (1940) believed that if the patient did not improve after five days' treatment with sulphathiazole, sulphadiazine should be substituted after an interval of two to three weeks. In our experience, however, this observation was not substantiated, as the subsequent analysis of the results will show. Sulphathiazole-resistant cases also appeared to be resistant to sulphadiazine, but penicillin provided the remedy on these occasions. A change from sulphonamides even to oestrogens was found more satisfactory than merely changing the type of sulphonamide.

Of the 83 cases presented in this series permanent recovery was obtained in 76 cases (91·5%). Progressive diminution of the coccal flora of the vagina and disappearance of the polymorphonuclear cells and macrophages were the characteristic features. Diphtheroids and certain strains of *E. coli*, however, persisted or appeared simultaneously with the disappearance of the pathogenic cocci. The change was observed on the second day in 69 out of 76 cases cured. In the remaining seven cases this change was noticeable between the third and fourth days. Once this change appeared the progress was steady and rapid. With complete recovery the vaginal secretion was found to consist of a few polymorphs and lymphocytes, immature vaginal epithelial cells, diphtheroids, *E. coli*, and occasionally enterococci and faecal streptococci.

The reaction of the vaginal secretion was also tested, but the only change which was noted was a diminution in the degree of alkalinity. The lowest *p*H recorded during sulphonamide treatment was 6·8. All the cured cases settled down to a *p*H of 7·2 to 7·5.

Failures were much less common than after oestrogen treatment, and the failure rate was 2·5%. In these two cases the symptoms were markedly ameliorated, and the vaginal discharge became scanty and white. Culture was positive in both. Obviously, an outcome like this is more dangerous than a frank failure, for the symptomatic relief may be mistaken for a cure while the child still remains a carrier and a source of potential danger.

In five cases (6%) the recovery was only apparent, for the condition relapsed. The interval between the apparent recovery and recurrence was eight days in one case, 12 to 13 days in three cases, and 17 days in the remaining one. In three out of these five cases the material collected from the rectum was negative for gonococcus on culture at the time of relapse.

All these seven cases where sulphonamides failed to establish a cure were put on a second course of the drug after an interval of three weeks (Table 9).

With a second course of treatment in the failure or relapse cases only one out of seven was cured. The other six were subsequently treated with oestrogens and penicillin with recovery in all cases.

Penicillin Therapy

Penicillin has been given ample trial in the treatment of gonorrhoea and found uniformly satisfactory. For this reason it was employed in the treatment of 35 cases of vulvovaginitis.

TABLE 9
ANALYSIS OF FAILED SULPHONAMIDE CASES

First Course of Sulphonamide	No. of Cases	Second Course of Sulphonamide	Result	
			Recovery	Failure
Sulphathiazole	2	Sulphadiazine	–	2
Sulphathiazole	2	Sulphapyridine	1	1
Sulphadiazine	1	Sulphathiazole	–	1
Sulphadiazine	2	Sulphapyridine	–	2

In the earlier part of the investigation the drug was given by three-hourly intramuscular injections but the treatment was found to be painful. In the last 20 cases penicillin was administered locally in the form of a jelly, the drug being introduced into the upper part of the vagina every three hours by means of an applicator of the type supplied with contraceptive jellies.

The dosage employed was the same for both intramuscular and local treatment, 10,000 Oxford units being given every three hours, one nocturnal dose being omitted. The vaginal jelly was made by adding mucilage of tragacanth and glycerine to concentrated penicillin solution in the proportion of 4:1 in order to make a concentration of 10,000 units per ml. The solution was loaded in a syringe and kept in a refrigerator. The applicator was sterilized each time after use and kept separately. With sensible and educated parents the instillation of this penicillin jelly into the vagina every three hours has never caused any difficulty.

In general, the results obtained were very gratifying. The course of treatment necessary was short, the average being 4·1 days. In two cases positive culture persisted in spite of eight days' continuous treatment and a total dosage of over 560,000 units. These have been regarded as failures.

The course taken by the disease treated with penicillin follows closely that under sulphonamide treatment. Enterococci and anaerobic streptococci persisted in all cases even after complete disappearance of gonococci. In all instances of recovery, the *p*H of the vagina settled down to $7 \cdot 2 \pm 0 \cdot 2$. Rectal infection appeared to be slightly more persistent than that in the vagina, as in none of the cases studied did the rectum become negative on culture at the same time as the vaginal culture, and required 24 to 36 hours' further treatment. This applied equally to local and parenteral penicillin. In local penicillin therapy the rectum was also treated in the same manner as the vagina, i.e. by instillation of penicillin jelly with a separate applicator inside the rectum, about $\frac{3}{4}$ to 1 inch above the anal margin.

The immediate recovery rate was 94·3%, i.e. 33 out of 35 cases. This, however, did not represent the permanent recovery rate, for in two cases mild relapse was noticed. Reappearance of symptoms occurred in both cases within two weeks of the suspension of treatment. The clinical manifestations of relapse in both of them were of a mild nature. These patients were put on further courses of penicillin, but even with three full courses recovery did not occur. Each repeated course of penicillin brought about a temporary relief of symptoms, but neither smear nor culture was negative. These were probably examples of penicillin-resistant gonorrhoea. Taking into account these cases the corrected recovery rate was 88·6%.

Treatment of Relapse and Failure Cases

In our series of 240 cases, 42 (17·5%) fell into this unfortunate category. It will appear that the incidence of such cases was low in the penicillin and sulphonamide treated groups, whereas the orthodox and oestrogen treatment showed higher figures. It was found that repetition of the same line of treatment did not produce satisfactory results. The general principles which were followed are: (1) Oestrogen-resistant cases were put on a course of sulphonamides after a period of rest for two weeks, during which period nothing more than general cleansing was done. (2) Sulphonamide-resistant cases were put on penicillin and vice versa after a similar period of rest for two weeks. (3) As soon as the infection appeared to be coming under control in either group of cases, oestrogens were administered with a view to increasing the acidity and the local resistance of the vagina. This last measure was found to be immensely helpful as the results will show.

It will appear that by combined treatment in which oestrogens played a not negligible role, a total salvage of 41 out of 42 cases was obtained and a recovery rate of 98·6%. It will also appear that without combined oestrogen treatment there was generally a greater tendency to relapse.

TABLE 10
ANALYSIS OF DRUG RESISTANT CASES

Nature of Drug Resistance	No. of Cases*	Nature of Drug Employed	No. of Cases	Cure	Relapse	Failure
Oestrogen	31 (30·4%)	Sulphonamide	11	5	4	2
		Sulphonamide and oestrogen	20	19	–	1
Sulphonamide	14 (15·5%)	Penicillin and oestrogen	5	3	1	1
Penicillin	6 (14·6%)	Sulphonamide and oestrogen	6	5	1	–

* This number totals more than 42, as failures in one group are included in the next.

Subsequent Fate of Children with Vulvovaginitis

Oestrogens, penicillin, or sulphonamides frequently cure the vulvovaginal infection, but the question is: ' Will there be any relapse or recurrence after puberty, and will the disease in any way interfere with the future process of conception ? '

This is an important sociological problem, so as many cases as possible were followed up through puberty and early married life.

It was found that 54 out of 78 traceable patients had attained puberty and menarche. Of these, 23 were married for a period of one to five years. Eighteen among the married group conceived within two to three years of marriage. Of the remaining five who did not conceive, four were married for less than two years and one was seeking treatment in a sterility clinic. It may be of interest to point out that one of those who conceived normally had developed signs of upper genital tract infection during the attack of vulvovaginitis. Though no positive conclusion can be arrived at, one may presume that the effects of vulvovaginitis on subsequent reproductive functions are not of considerable importance. Enquiry was made also about the menstrual history, but nothing outstanding was discovered, which could be due to the infection in childhood. Investigation, however, revealed that 71 among 78 cases traced showed considerable sex consciousness dating from soon after the disease. Records showed that 60 out of these 71 cases had undergone energetic local treatment. This is a mild warning against the indiscriminate use of intensive local treatment in vulvovaginitis of young children.

Summary

Gonorrhoea accounts for probably not more than half the cases of vulvovaginitis in infants and children. Neither oestrogens nor penicillin nor sulphonamides offer an absolute therapeutic remedy. No matter what treatment is employed a certain number of cases appear to be resistant. With oestrogens a 72 to 75% cure is about the average which can be expected. With penicillin and sulphonamides a 90% recovery rate is a modest expectation. A comparative study of the results obtained with these three therapeutic measures is tabulated (Table 11).

The difference between results obtained with sulphonamides and penicillin is not striking. Sulphonamides, however, possess some toxicity and as such sulphonamide treated cases require to be watched carefully. The duration of treatment is about the same in both cases. Penicillin is at present expensive and the frequent medication necessarily is a drawback. The results of local penicillin treatment have been very encouraging and can be depended upon if the parents can cooperate.

Oestrogens also possess a distinct place in the treatment of vulvovaginitis. With the use of synthetic drugs expense is not a serious problem,

TABLE 11
COMPARATIVE STUDY OF RESULTS WITH OESTROGENS, SULPHONAMIDES, AND PENICILLIN

Nature of Therapy	Percentage of Cases*	Average Duration of Treatment	Cure (%)	Relapse (%)	Failure (%)
Oestrogens ..	42·5	5-6 weeks	75·5	13·7	10·8
Sulphonamides ..	34·6	5-9 days	91·5	6·0	2·5
Penicillin ..	14·6	4·1 days	88·3	5·7	5·7

* Twenty cases treated with local antiseptics only are not included.

but the course of treatment is prolonged and the recovery rate lower than with either sulphonamides or penicillin. The value of oestrogen therapy is, however, considerably increased in the treatment of relapsed or refractory cases. It is in these that the combination of oestrogens with either sulphonamide or penicillin is almost always rewarded with success.

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OSTEOMYELITIS IN THE NEWBORN

BY

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The earlier literature on osteomyelitis of very young infants dealt largely with osteomyelitis of the jaw and its probable relationship to mastitis in the nursing mother (Marx, 1920; Bass, 1928; Karplus, 1928; Wilensky, 1932; Poncher and Blayney, 1934).

Metastatic osteomyelitis due to umbilical sepsis was mentioned by Fraser (1924) who collected some 30 cases over a period of four years. He said that a fatal result was almost inevitable. Baumgartner (1920) recorded a case of osteomyelitis of the skull, Madier (1922) one of osteomyelitis of a vertebra, and Palew (1931) one of gonoccoccal osteomyelitis.

In a study of septicaemia of the newborn infant Dunham (1933) found that osteomyelitis occurred in 10·3% of the cases and that three out of four such cases died. Mount (1935) reported a fatal case of septicaemia with osteomyelitis of the humerus. Green (1935) recorded a case of osteomyelitis of the humerus, with recovery, where the original lesion may have been a furuncle of the chin at the age of two weeks. The same author with Shannon (1936) published a series of 23 cases of osteomyelitis which occurred before the age of six months. The mortality rate was 45%. They related extra-osseous infection and trauma to the osteomyelitis and stressed skin infection and omphalitis as primary lesions. They considered that osteomyelitis was not a rare disease in infants and emphasized that the treatment was that of the general condition rather than of the local one.

The poor prognosis given by Fraser and Dunham was not confirmed by Dillehunt (1935) among whose cases there were two in the neonatal period. He said:

> 'The disease is rare in infants. It is relatively benign, and neglect to treat it in infants is less harmful than in adults. The prognosis is favourable. Sequestra do not form. Spontaneous resolution without treatment may occur. Foci of infection may become sterile.'

In the three cases recorded by Cass (1940) there was relatively little systemic disturbance though in two of them there was pyrexia. Apart from deformity, the prognosis was stated to be good in the absence of infection of the lungs, peritoneum, meninges or skin. Four cases of osteomyelitis all of which recovered were recorded by Stone (1942). He stated that the course of the disease in the newborn was benign and that the treatment of the osseous lesion was of secondary importance. He gave a good prognosis for life and function.

The benign course of the disease was also mentioned by Einstein and Thomas (1946) who said that involvement of a joint was common and was the most serious complication. Of their ten cases under the age of six months one was in the neonatal period. A case of osteomyelitis with recovery in a 19-day old infant was reported by Shulman (1946).

The confusion of opinion in the prognosis of osteomyelitis was in large measure clarified by Greengard (1946). He recorded ten cases of acute haematogenous osteomyelitis in infants, one of which was in the neonatal period. He suggested that in the newborn infant there were two forms of this disease; first, a ' benign ' form in which there was little or no complaint other than local disability and no history of preceding illness, and second, a severe form in which there was systemic evidence of a violent infection and the local disease made its appearance as a complication. In this latter group the mortality was high. Hutter (1948), recording three cases of neonatal osteomyelitis, agreed with Greengard's classification.

Because of the number of cases of osteomyelitis in the neonatal period which have been recorded it may be said that this disease should no longer be considered a rare one: yet it has seldom been reported from a maternity hospital. The four cases now recorded were prematurely born infants who from birth were under the daily care and supervision of a paediatrician. Thus the earliest clinical manifestations of morbidity were observed.

Case Reports

Case No. 1. This immature male infant, the result of a ninth pregnancy, was born spontaneously of unrelated parents on July 5, 1943. He weighed 5 lb. 7 oz. at birth. Progress was normal until the ninth day when onychia of the right middle finger was observed. Despite local treatment with gentian violet and fomentations, and chemotherapy with sulphathiazole g. ¼ four-hourly, the inflammation spread. The finger, and finally the whole hand, was involved. A discharge of thin pus came to the surface over the dorsal aspect of the distal joint of the finger which was incised. The pus was not investigated bacteriologically. The sinus was healed four weeks from the appearance of the onychia, when all swelling had disappeared except that affecting the finger. At this stage the finger was examined radiologically (Fig. 1). Almost complete destruction of the bone of the middle phalanx and most of the proximal part of the distal phalanx was seen.

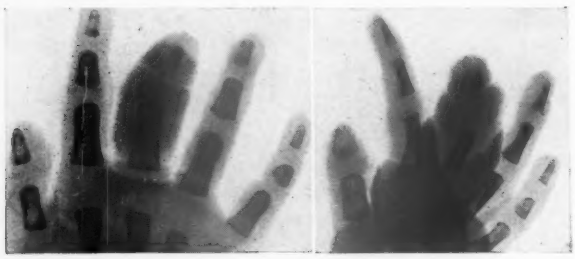

FIG. 1.—Radiographs showing pinpoint of bone in the middle phalanx and considerable destruction of proximal portion of distal phalanx.

The infant was discharged aged 45 days. He weighed 6 lb. 3½ oz. No systemic disturbance occurred during this acute illness (Fig. 2).

The infant has been observed at intervals since discharge from hospital. A radiograph shows the extent of bone recovery at the age of 5 years and 7 months (Fig. 3).

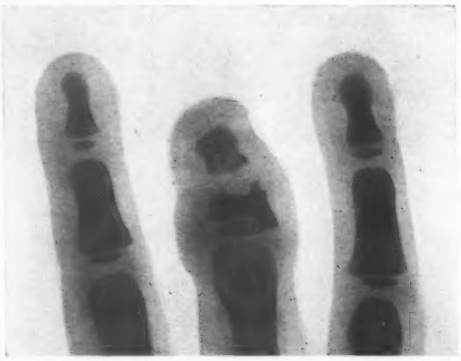

FIG. 3.—Radiograph showing extent of bone recovery.

Case No. 2. This female infant was born spontaneously on January 13, 1943. She weighed just over 5 lb. At 12 days staphylococcal pustules were seen in the right axilla and at the right elbow. They were treated with a 1% aqueous solution of gentian violet. From the pustule at the elbow inflammation spread rapidly into the soft tissues. A fluctuating swelling near the proximal end of the ulna and on the dorsal aspect was incised on the eighteenth day. From the pus thus obtained *Staphylococcus aureus* was grown. A diagnosis of periostitis or osteomyelitis was made three days later, but was not confirmed on radiological examination. During the period of clinical inflammation there was virtually no general systemic disturbance (Fig. 4). When 54 days old a second radiograph of the elbow joint region confirmed the original diagnosis of osteomyelitis (Fig. 5).

The infant made good progress and an uneventful recovery. Excellent functional use of the arm has been obtained, so that at 6 years old pronation and supination were complete. The only disability was a limitation of flexion at the elbow (Fig. 6).

Case No. 3. Born on January 30, 1947, this spontaneously delivered immature male infant weighed 3 lb. 2½ in. There was slight oedema of the legs, but the general colour was good and breathing was

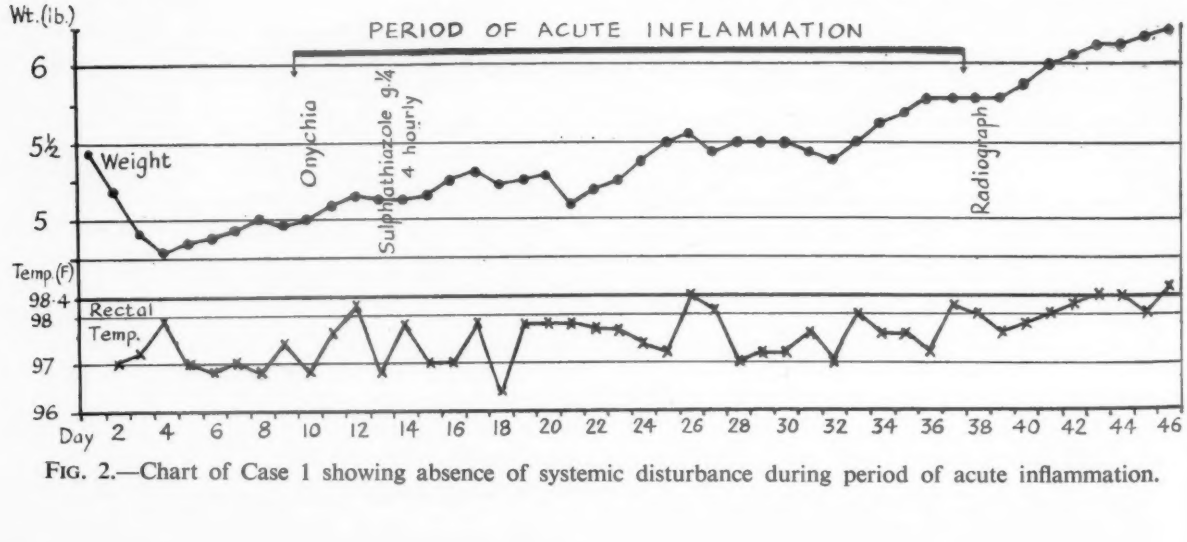

FIG. 2.—Chart of Case 1 showing absence of systemic disturbance during period of acute inflammation.

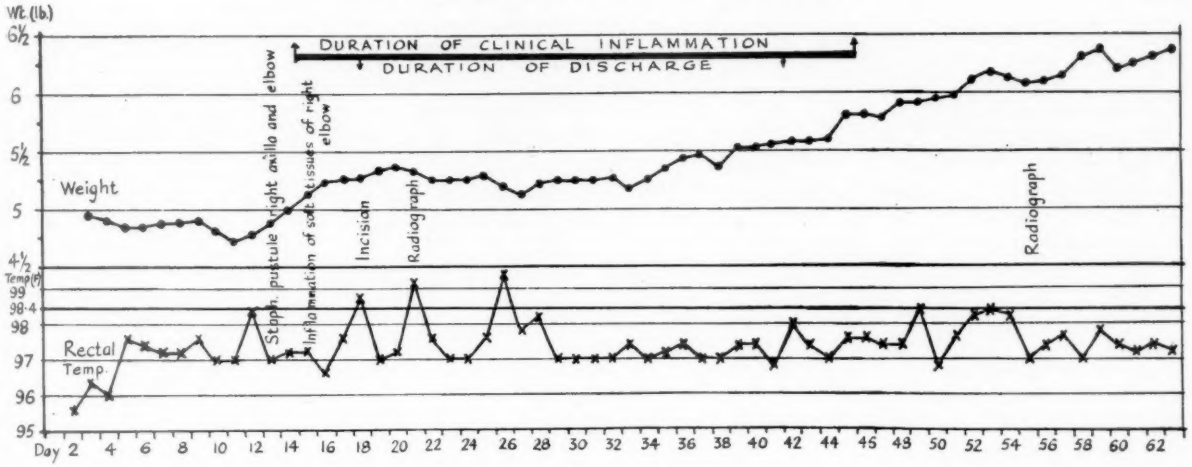

FIG. 4.—Chart showing only slight halt in weight gain and virtual absence of pyrexia. There was no general systemic disturbance.

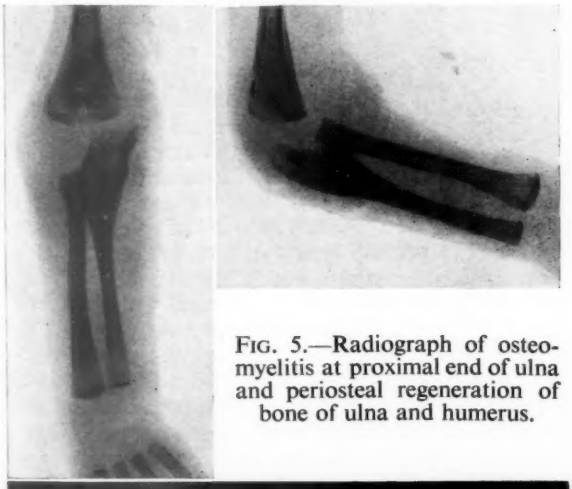

FIG. 5.—Radiograph of osteomyelitis at proximal end of ulna and periosteal regeneration of bone of ulna and humerus.

FIG. 6.—Limitation of flexion at elbow.

satisfactory. Because there was gastro-enteritis in the unit when the infant was born he was given sulphaguanidine as a prophylactic measure. The infant was fed by gavage and made satisfactory progress. On the night of the thirteenth day respirations became rapid and shallow and there was some vomiting. Though on clinical examination no other abnormality was discovered, a respiratory infection was presumed and penicillin and sulphathiazole were exhibited from the fourteenth day onwards (Fig. 7). Crepitations were heard in the right lung on the following day and x-ray examination suggested bronchopneumonia.

Swelling over the anterior and superior aspects of the left shoulder was seen on the sixteenth day. On aspiration, blood-stained pus was obtained and from it *Staphylococcus pyogenes albus* was grown. It was insensitive to penicillin. An identical organism was cultured from the blood on the twentieth day. On the same day small septic spots appeared on both arms and became haemorrhagic. The presence of osteomyelitis of the head of the left humerus was shown radiologically on the twenty-second day (Fig. 8). At the same time a localized inflammatory reaction developed in the left ankle and four days later the proximal end of the left tibia was involved. Osteomyelitis of the tibia was demonstrated radiologically (Fig. 9), but the same clinical diagnosis for the ankle was not confirmed. The shoulder region, which had been aspirated three times, was opened and drained on the thirty-first day, when the ankle was similarly dealt with. On the following day loose green stools appeared and sulphaguanidine medication was begun, but stopped in four days when these signs had disappeared. There was now little discharge from the shoulder and none from the ankle. A respiratory infection was still manifest in a nasal discharge. This became more profuse on the day of death when crepitations were again heard in the right lung. A severe cyanotic attack occurred and when this recurred the infant died, on the thirty-ninth day.

Necropsy and histological examination were performed. The findings were as follows:

RESPIRATORY SYSTEM. A resolving pneumonia of haematogenous origin, and minute, apparently quiescent, pyaemic abscesses in both lungs.

LOCOMOTOR SYSTEM. Osteomyelitis of the head and neck of left humerus. Left shoulder joint intact, but distended with pus. Osteomyelitis of the proximal end

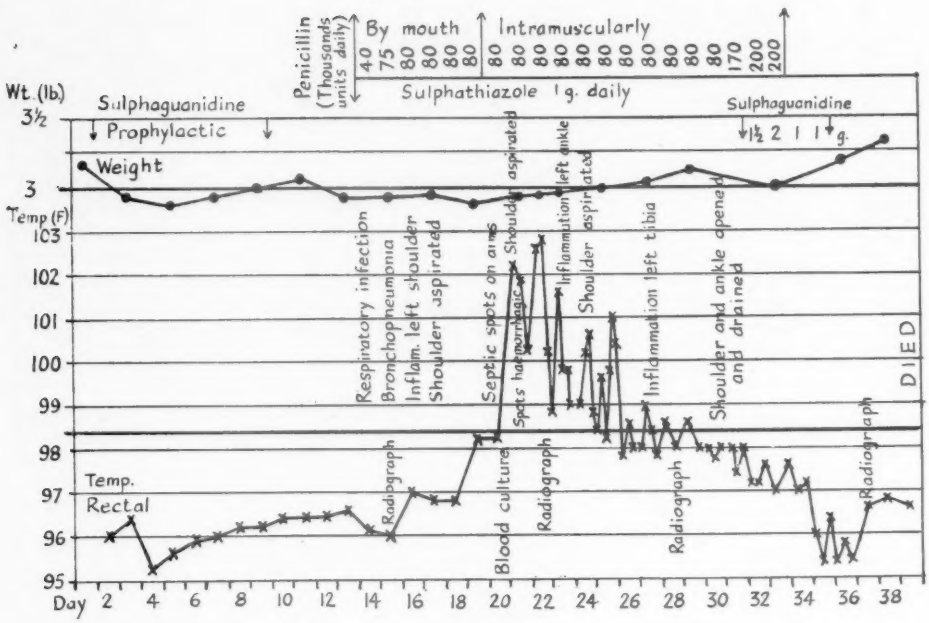

FIG. 7.—Chart showing general systemic disturbance.

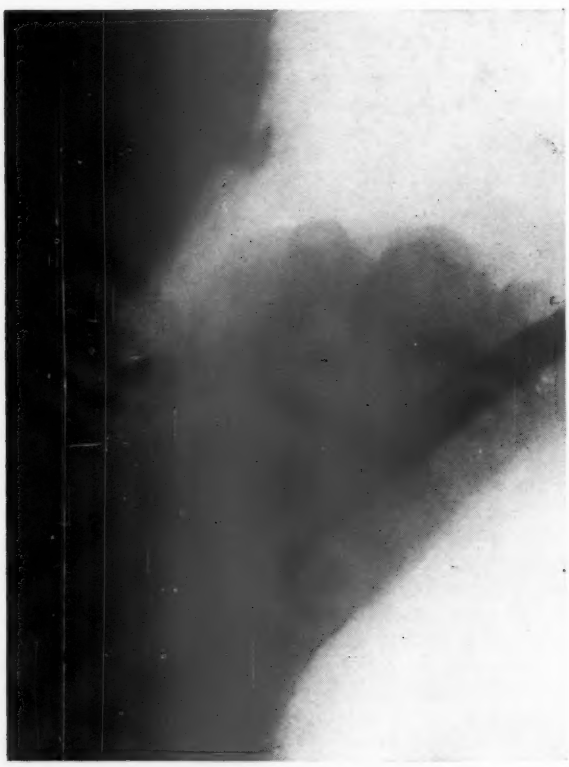

FIG. 8.—Osteomyelitis head of left humerus.

of the left tibia. Purulent arthritis of the left ankle joint and left tarsal joints.

Case No. 4. This male infant was spontaneously delivered on November 11, 1948. He weighed 5 lb. 2¾ oz.

Progress was satisfactory until the fifteenth day when irritability and anorexia were observed. On clinical examination only mild paronychia of the left fifth toe was observed. Oral penicillin, 30,000 units four-hourly, was prescribed. Pyrexia and loss of weight occurred in the next 24 hours (Fig. 10). The infant appeared grey and toxic. The eyes were sunken. There was localized inflammation over the right medial malleolus, and movement of the ankle caused the infant to cry. On the third day of the illness pus was aspirated from the ankle and a culture of penicillin-resistant *Staphylococcus aureus* was obtained. At the same time the left wrist was inflamed. Oral penicillin was changed to intramuscular injections of 100,000 units three-hourly. On the fifth day of illness a swelling on the anterolateral aspect of the upper third of the right thigh was aspirated and thick pus obtained. By this time the inflammation of the left wrist subsided, but the right ankle remained swollen and fluctuating. Oral penicillin, 200,000 units three-hourly, was given again. Some clinical improvement in the child's condition was apparent at this time, and despite the persistence of pyrexia the improvement was maintained. He lost the grey appearance of a desperately ill infant. On the ninth day the localized swelling at the right ankle was incised, and from the pus a culture of *Staphylococcus aureus*, resistant to over 100 units of penicillin per ml. but sensitive to 2 units of streptomycin per ml., was obtained. The discharge from the ankle was persistent. A probe could be passed into the ankle joint.

X-ray examination on the fifteenth day showed destruction and dislocation of the head of the right femur (Fig. 11). An unsuspected lesion of the fourth right costochondral joint was also disclosed. The right leg was kept abducted and externally rotated with a Putti mattress splint. On the nineteenth day of the illness streptomycin medication was begun, and 100 mg. were given daily for nine days. All inflammation subsided rapidly and the infant made good clinical progress. A radiograph on the fortieth day of illness showed regeneration of bone (Fig. 12). The infant was discharged when 93 days old, and weighed 8 lb. 7½ oz.

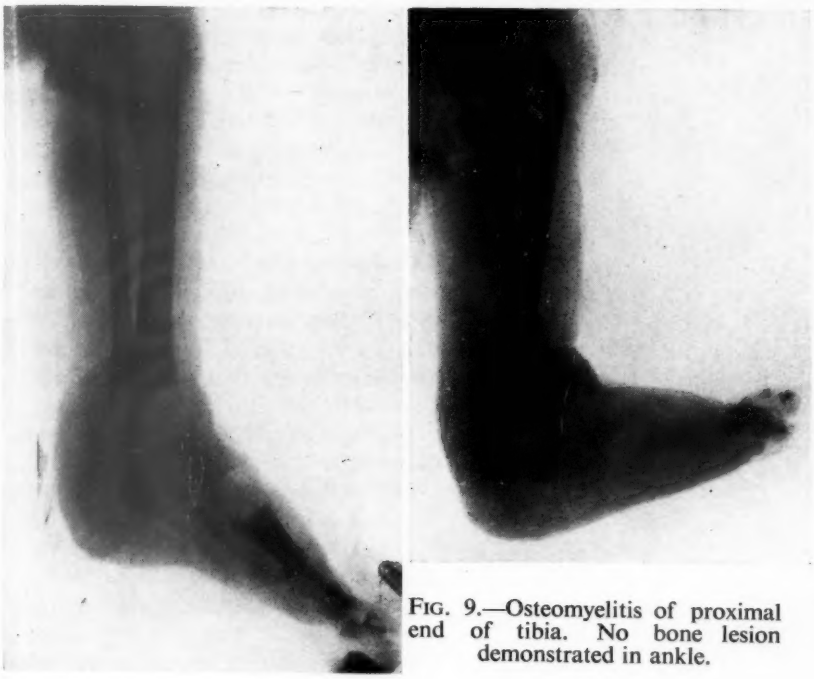

FIG. 9.—Osteomyelitis of proximal end of tibia. No bone lesion demonstrated in ankle.

The child's progress has been supervised at the infant welfare clinic during the first year of life, and he has also attended the orthopaedic department. There have been no illnesses. At one year old he weighed 19 lb. 4 oz., had five teeth, and was an alert, happy child who on the slightest provocation exhibited a strong desire to stand on his feet.

Radiological examination at this age showed that the right ankle joint had healed completely and had about 20 degrees of movement. There was no evidence of disease of the fourth right costochondral joint. There was complete destruction of the head of the right femur, some malformation of the proximal end of the shaft, and some upward displacement. The acetabulum was healthy (Fig. 13).

Discussion

The consensus of opinion concerning the aetiology of neonatal osteomyelitis is in favour of an antecedent infection. This may be omphalitis, as emphasized by Fraser, or a respiratory infection as in Case No. 3, or, most commonly, a skin lesion. Skin lesions are very prevalent in the newborn period and are invariably staphylococcal in type. Over a three-year period in a maternity hospital Henderson (1943) recorded 550 cases, an incidence of 6·8%. He reported no complications other than conjunctivitis, and there were no deaths. These lesions are usually small, few in number, and transient. The relative infrequency with which complications appear, and the ease with which the majority of these lesions yield to simple therapeutic measures, largely obscures the potential danger which exists in all such cases.

It is significant that all our four cases were

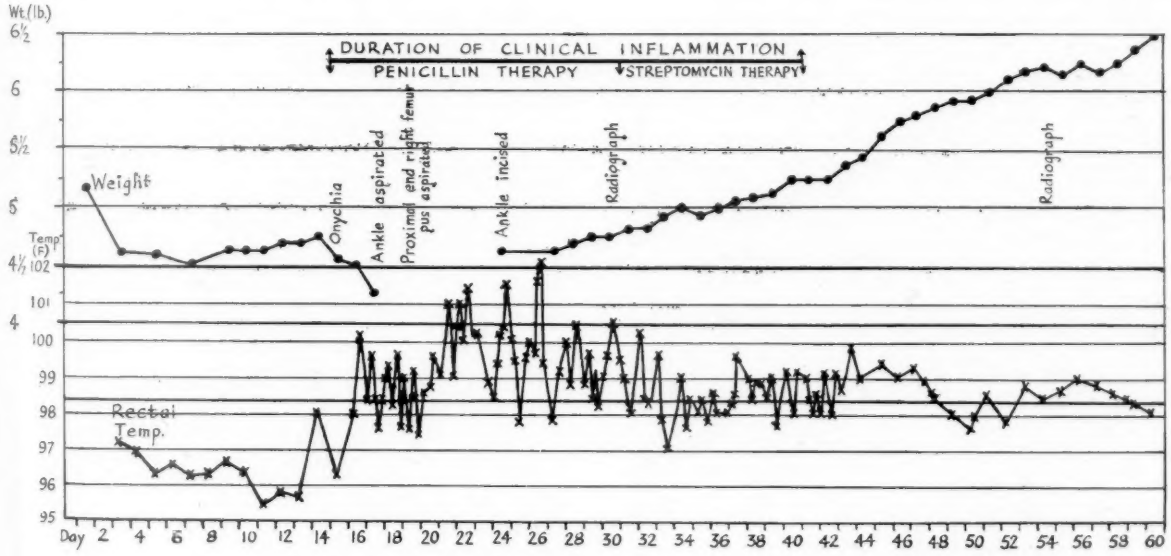

FIG. 10.—Clinical chart showing grossly abnormal temperature and weight loss at beginning of illness.

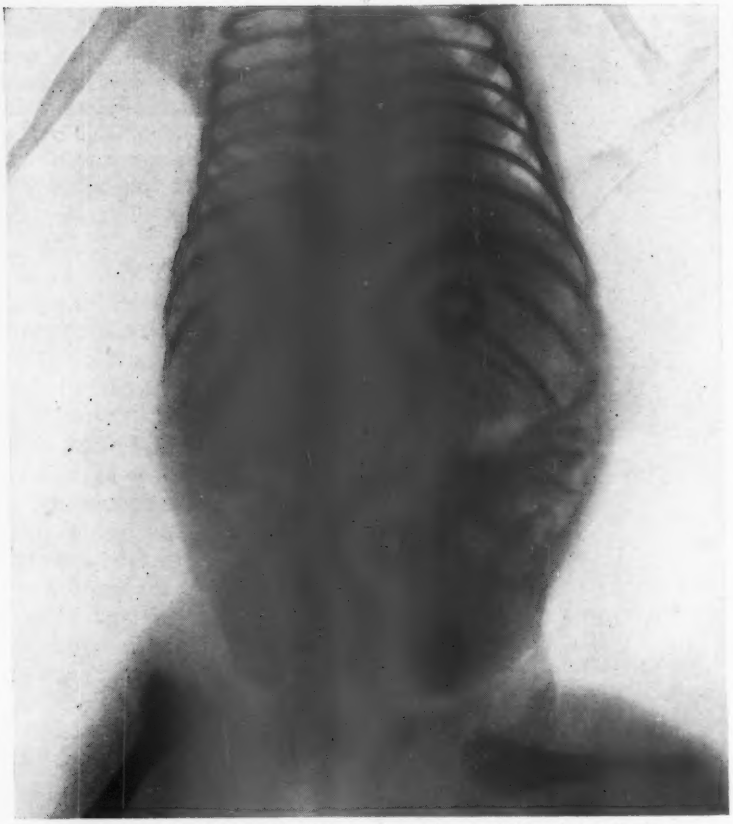

FIG. 11.—Radiograph illustrating rib and hip joint lesions.

immature infants. Such infants are immunologically immature, and not only much more susceptible to bacterial invasion than full-term infants, but also much less able to combat an established infection.

These four cases are divisible into two clinical groups. Cases 1 and 2 showed no systemic disturbance and ran a relatively mild or 'benign' course, whereas Cases 3 and 4 showed a gross systemic disturbance which ended fatally for one of them. This division of cases tends to confirm Greengard's clinical classification (1946), which is supported by Hutter (1948).

It can hardly be doubted that in Cases 3 and 4 the multiple osteomyelitis was a complication arising from a blood-borne infection. This may have been of respiratory origin in Case 3, and have arisen from skin infection in Case 4.

In Cases 1 and 2 a feature was the intimate relationship of the site of the osteomyelitis to the site of the initial inflammatory lesion in the soft tissues. The circumscribed nature of the lesion throughout the illness and the absence of any gross systemic disturbance might have suggested that one was dealing with a direct extension of a local inflammatory process. From this point of view it is unfortunate that no blood cultures were attempted in Cases 1 and 2. Moreover, any consideration of such a suggestion must be tempered by the knowledge that Hutter obtained positive blood cultures from a case of 'benign' neonatal osteomyelitis.

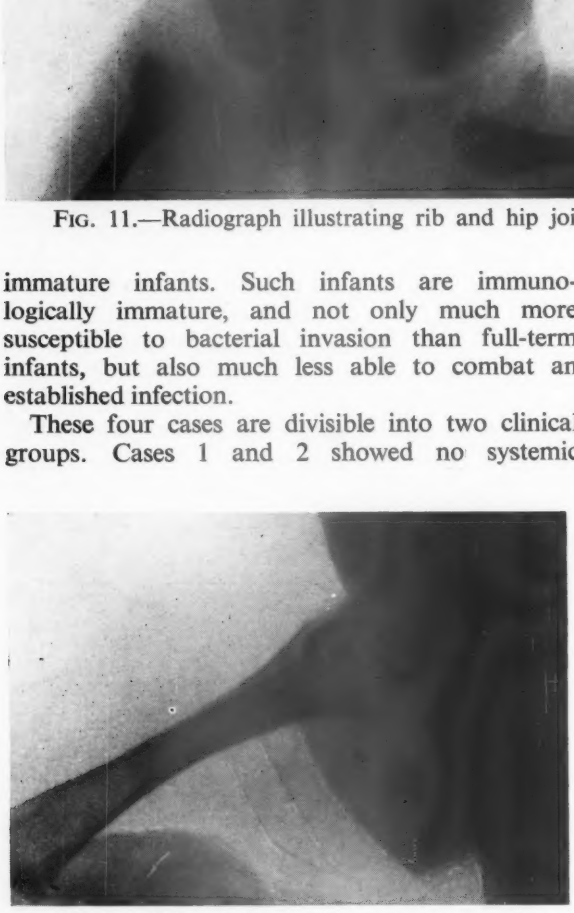

FIG. 12.—Radiograph illustrating regeneration of bone on the fortieth day of the illness.

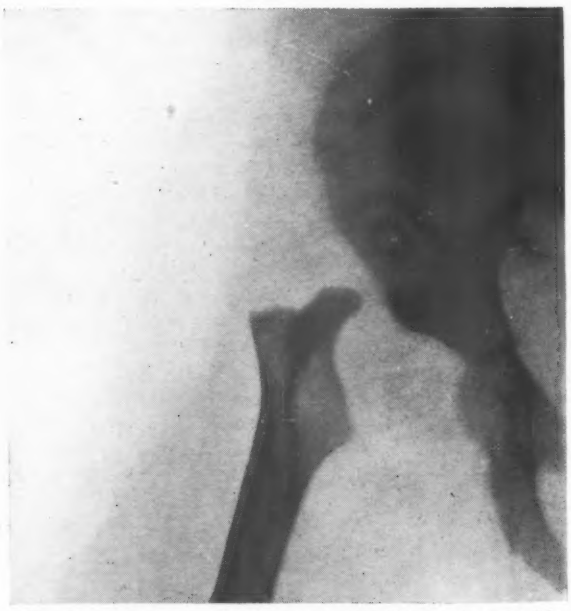

FIG. 13.—Radiograph showing condition of right hip joint at one year after illness.

The three surviving cases each show some degree of permanent disablement. The extent of the disability in Cases 1 and 2 is slight and the functional result is very good. These two cases resemble those described by Cass (1940), who pointed out the risk of deformity in mild cases, and those described by Einstein and Thomas (1946) who said that involvement of a joint was a common and serious complication in ' benign ' cases.

The degree of loss of function sustained from neonatal osteomyelitis is not determined by the ' benignity ' or otherwise of the course of the disease in the acute phase, but rather by the extent to which natural healing takes place and by the functional nature of the affected bone and joint. This is illustrated in Case 4 which shows the greatest degree of permanent disability of the three surviving cases. The much greater degree of disablement is caused by the destruction of a joint which should provide a high degree of stability. It is not possible in this case to assess the ultimate extent of the functional disability. It is hoped that much may be accomplished by orthopaedic means.

Because of the residual disability so often present in ' benign ' or mild cases, one feels that the term ' benign ' is a misnomer whose use should be discontinued. With this suggestion Greengard and Hutter are in agreement.

The high mortality rate hitherto recorded in neonatal osteomyelitis is not likely to continue, for the advent of chemotherapy and antibiotic treatment is exerting an ameliorating influence on the prognosis of this disease. This is well illustrated by Hutter, who records that during 1934-43 in the Children's Hospital, Los Angeles, there were 12 cases of haemolytic staphylococcal osteomyelitis in children under the age of six months. The mortality rate was 58%. In the subsequent period from 1943-47 there were six similar cases in the same age period. They were all treated with penicillin and chemotherapy, with no deaths.

The increase in the survival rate may result in the sequelae of neonatal osteomyelitis being seen more frequently in orthopaedic hospitals and clinics. This premise cannot be based on the small number of cases now recorded, but the two groups mentioned by Hutter offer highly suggestive evidence. In the 1934-43 groups none of the survivors showed residual deformity, but in the 1943-47 groups two-thirds of the survivors showed residual deformity involving one or more joints.

Summary

Four cases of neonatal osteomyelitis occurring in immature infants are recorded.

They are divisible into two clinical groups; one relatively mild, the other severe and carrying considerable risk to life.

The potential danger existing from staphylococcal skin lesions in the neonatal period is stressed and the particular susceptibility of the immature infant.

Attention is drawn to a probable increase in the number of cases of disability following neonatal osteomyelitis which may be seen in orthopaedic clinics.

The adjective term ' benign ' which has been applied to the mild group of cases is a misnomer.

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STAPHYLOCOCCAL PYAEMIA WITH PULMONARY AND COLD SUBCUTANEOUS ABSCESSES

BY

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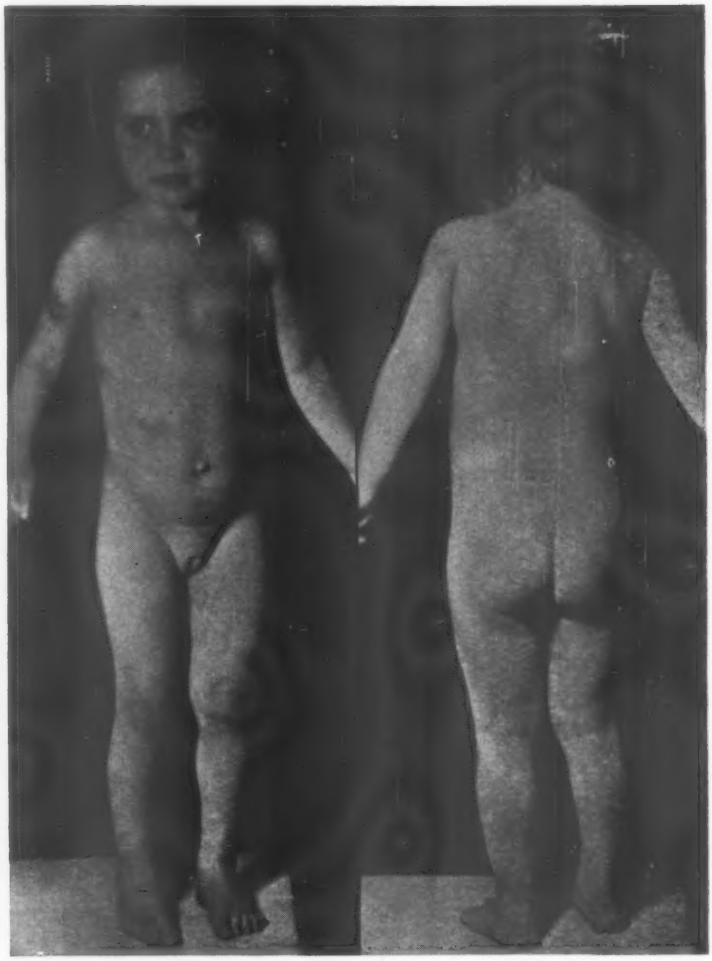
(RECEIVED FOR PUBLICATION NOVEMBER 4, 1949)

Staphylococcal pyaemia not infrequently complicates staphylococcal lesions, and it is not rare for it to give rise to metastatic abscesses in the lungs and subcutaneous tissues. The following case is considered worth recording, because the patient, a child of just under three years, presented with multiple cold subcutaneous abscesses apparently arising *de novo*, and unaccompanied by severe systemic manifestations.

Case Report

The patient, a girl of 2 years 11 months, was perfectly well until two weeks before admission to hospital. At that time she developed a sore throat, lost her appetite, and became moderately constipated. Her mother also noticed the appearance of a tender lump in the right hypochondrium, which was succeeded by the rapid appearance of similar swellings on the body, neck, and right arm. These lumps were tender, circumscribed, and increased progressively in size, with slight reddening of the overlying skin, but did not break down or discharge.

During the whole of this time the child's general condition remained good, apart from occasional transient bouts of abdominal pain, the development of an unproductive cough for seven days before admission, increasing pallor, and, for two days before coming to the hospital, obvious pyrexia and fretfulness.



a *b*

FIGS. 1*a* and *b*.—Photographs taken shortly after admission, showing the subcutaneous abscesses. The one overlying the lower right ribs in the mid-axillary line has been aspirated. Those on the back show well the absence of change in the skin. In Fig. 1*a* the small scar over the left patella can be seen.

The only significant observation in the past history was an abrasion of the left knee three or four weeks before the onset of symptoms. There was no sickness in any other member of the family, a brother of six years and a sister one year being well.

On admission (April 16, 1949) the child's temperature was 102°F., and she was pale and fretful, but did not appear acutely ill. The tonsils were enlarged and injected, but no exudate was seen. There were a few shotty glands in the left cervical lymphatic chain. Multiple lumps

(Figs. 1*a* and *b*) were present in the subcutaneous planes of the neck, thoracic wall, anterior and posterior abdominal walls, and the right upper arm. The swellings in the right arm, left neck, right lower anterior thoracic wall and right hypochondrium showed a dusky reddening of the overlying skin. All the lumps were slightly tender on palpation, were well defined, cold, and seemed to be subcutaneous. The lumps in the right lower anterior thoracic wall and in the posterior fold of the left axilla were fluctuant. There was a small healed abrasion on the left knee. No other clinical abnormalities were detected.

The swelling in the right lower anterior thoracic wall was aspirated and blood-stained purulent material was withdrawn. Examination of this showed numerous pus cells with a moderate number of Gram-positive cocci, culture yielding a moderate growth of *Staph. aureus*. A throat swab produced a mixed growth with a few colonies of *Staph. aureus*. A catheter specimen of urine and a blood culture were sterile, and a tuberculin jelly test was negative. The total white cell count was 8,700 per c.mm. (90% polymorphs, 4·5% lymphocytes, 1% monocytes, and 4·5% metamyelocytes). A chest radiograph revealed ill-defined, rounded opacities at the left base and right apex having the radiological appearance of pyaemic abscesses.

Penicillin was given intramuscularly beginning with 250,000 units, then 100,000 units three-hourly for four days, and 40,000 units four-hourly for a further two weeks.

A blood count on April 20, 1949, showed: red corpuscles, 4,800,000 per c.mm.; Hb., 68%; C.I., 0·71; white corpuscles, 26,000 per c.mm. (polymorphs, 67%).

Subsequently ferri et ammon. cit. gr. 2½ t.d.s., 'adexolin' m. 5 b.d. and ascorbic acid mg. 25 b.d. were administered. The abscess over the posterior wall of the left axilla was aspirated on April 21 and thick creamy pus, which yielded a heavy growth of *Staph. aureus* obtained.

On April 22 the subcutaneous abscesses were incised and drained, yellow pus being evacuated, and the cavities packed with vaseline gauze wicks after dusting with penicillin and sulphonamide powder. The post-operative improvement was rapid and all the wounds healed cleanly within a few days.

A second chest radiograph on May 4 showed resolution of the abscesses at the right apex, but little change in the radiological appearances at the left base. The patient was discharged home on May 12.

Discussion

Reference to the literature confirms the rarity of cold staphylococcal abscesses, and in the 15 years 1923-38 (that is the period immediately before the introduction of sulphonamide therapy) I have been able to find only four reports of single subcutaneous abscesses simulating cold tuberculous abscesses (Milian, 1932; Oury and Le Bars, 1935; Scollo, 1935) and none of multiple lesions.

In the present case the differential diagnosis lay between multiple tuberculous abscesses; multiple pyogenic abscesses; and multiple lipomata.

The pyogenic nature was demonstrated by the isolation of the causative organism and the response to penicillin and surgery. It is uncertain whether the primary focus of infection was in the throat or the abrasion over the left patella.

It is interesting to note the failure of the reactive and immunological body processes as shown by the absence of marked inflammation (that is, no heat, and but slight redness and pain) and the low white count (8,700 per c.mm.) together with minimal general upset. It is significant that, after four days' massive penicillin therapy, the total white count had risen to 26,000 per c.mm.

Another observation of some moment was the extent of the lesions in the lungs without any clinical signs of their presence apart from an unproductive cough.

I am grateful to Sir Cecil Wakeley, under whom the child was first admitted, and to Dr. W. Sheldon, to whose care she was subsequently transferred, for permission to publish this case history. I am also indebted to Dr. Sheldon for his help in the preparation of this paper.

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THE PROGNOSIS OF PNEUMONIA IN INFANCY AND CHILDHOOD

BY

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The use of the sulphonamides and penicillin in the therapy of pneumonia and bronchopneumonia in children has considerably altered the prognosis in these diseases. Although there are reports on the results of treatment with various sulphonamides, there are only a few published studies on the response to treatment with penicillin alone or with penicillin and sulphonamides combined. It was felt, therefore, that a survey of the results of treatment of pneumonia during the past three years at two children's hospitals might be of value in assessing the therapeutic efficiency of methods currently employed.

The records of all pneumonia cases admitted to the Royal Manchester Children's Hospital and to the Duchess of York Babies Hospital during 1946, 1947, and 1948 have been examined. The clinical diagnosis in all cases included in this study was confirmed radiologically and, in the event of death, by necropsy. Two hundred and fourteen cases were thus surveyed.

The overall mortality in this series (Tables 1 and 2) with all forms of treatment was 17% (33 of 194 cases). This rather high mortality is accounted for by the large number of infants under six months of age. Figures given by Scandinavian authors varied from 22% (Friedlander, 1931) to 14% (Lichtenstein, 1939; Vilen, 1942), while in this country mortality figures of 17% in 1937 (Gaisford, 1940) and 18% in 1939 (King Lewis, 1944) were recorded. More recently a fatality rate of 28% from bronchitis and pneumonia in infants under one year of age for the period 1946-1948 was given by Smellie (1949).

In the present series, excluding the cases under

TABLE 1

ANALYSIS OF 194 CASES, SHOWING AGE DISTRIBUTION, TREATMENT, AND RESULT

Treatment	Age					Result	
	0–6 (months)	6–12 (months)	1–2 (years)	2–5 (years)	5–10 (years)	Recovery	Death
Sulphonamide ..	18	9	17	4	7	48	7
Penicillin	22	12	6	13	10	51	12
Combined therapy ..	36	20	10	6	4	62	14
Total	76	41	33	23	21	161	33

TABLE 2

ANALYSIS OF 33 DEATHS ACCORDING TO AGE AND TREATMENT

Treatment	Age					Total
	0–6 (months)	6–12 (months)	1–2 (years)	2–5 (years)	5–10 (years)	
Sulphonamide ..	5	1	0	1	0	7
Penicillin	12	0	0	0	0	12
Combined therapy ..	11	3	0	0	0	14
Total	28	4	0	1	0	33

six months of age, there were only five deaths in 118 cases (4%). The mortality rate, therefore, over six months of age, whatever method of treatment be used, is low and a favourable prognosis may be expected.

In striking contrast, the mortality under six months of age is still very high. Reviewing all forms of treatment it was found that there were 28 deaths among 76 infants, a mortality rate of 36%.

Considering the sulphonamide-treated group under six months of age, five deaths (27%) occurred among 18 cases. King Lewis (1944) in a comparable group found a mortality of 11·1% (three deaths out of 27 cases). Using sulphapyridine Greengard, Raycraft, and Motel (1941) reported a mortality of 12% in infants under three months and 16% in those from three to six months of age. Gaisford (1940) reviewing 178 cases of bronchopneumonia in children of all ages treated with sulphapyridine recorded an overall mortality rate of 8·4%. Analysis of these figures (Gaisford, 1939), however, shows that of 11 cases under six months of age five died (45%) and that there were five deaths among 40 cases in the six to 12 months age group (12·5%). Between the ages of one and two years there were four deaths among 50 cases (8%) but there were no fatalities in the older age groups.

A combination of sulphonamides and penicillin does not appear to be any more effective than either drug used separately. Among 36 cases treated with such a combination there were 11 deaths (30%). Thus, no benefit can be claimed for the added penicillin.

Furthermore, considering the mortality figures at all ages, the highest percentage of deaths occurs in the under six months age group, while between six months and one year there is already a considerable diminution in these figures. Over one year of age there was only one death out of 77 cases (1·3%). Reviewing the age distribution of deaths from pneumonia in the whole of Manchester over a similar period, it can be seen (Table 3) that the greatest number of deaths again occurs in the under six months age group, while in the second half of the first year there is a marked decrease in the death rate. During the remainder of childhood the mortality figures are very low. The hospital figures therefore reflect the general mortality trend for the whole area of Manchester, although older children and milder cases in infancy are usually treated in their homes, and only the more severe cases are now sent to hospital.

TABLE 3
DEATHS FROM PNEUMONIA IN MANCHESTER

Year	Age				
	0–6 (months)	6–12 (months)	1–2 (years)	2–5 (years)	5–10 (years)
1946	91	26	15	2	1
1947	121	32	13	5	0
1948	85	22	8	6	0
Total	297	80	36	13	1

It is therefore obvious that any attempts to reduce the mortality rate from pneumonia must be directed towards improved treatment during the first six months of life. As new and more powerful antibiotics, with varying ranges of specific action, come into use, a closer study of the aetiological organism responsible for the pulmonary infection may help to improve the response to treatment, as it is possible that sulphonamide- and penicillin-insensitive organisms may account for a proportion of the pneumonias occurring in this age group. Although it is extremely difficult to obtain sputum for bacterial examination from infants, culture of a post-nasal swab, particularly one taken after a bout of coughing, may reveal a predominating organism which can with a fair degree of probability be regarded as the chief pathogen, and so indicate the appropriate specific treatment (Alexander, Craig, Shirley, and Ellis, 1941; Olshaker, Ross, Recinos, and Twible, 1949). A big disadvantage, however, is that some time must elapse before this specific therapy can be started.

TABLE 4
ANALYSIS OF 20 DEATHS WITHIN 24 HOURS OF ADMISSION

Age					Total
0–6 (months)	6–12 (months)	1–2 (years)	2–5 (years)	5–10 (years)	
15	3	1	0	1	20

Twenty children died within 24 hours of admission (Table 4), many only a few hours after their arrival in hospital, and these cases warrant separate consideration as they form almost 38% of the total number of deaths. The age distribution follows the general pattern so far demonstrated with the highest number in the under six months group, and a rapid decrease in number in the second half of the first year of life. An attempt was made to elicit any factors which might possibly account for the admission of so many children in a moribund state. Seven such infants had been ill for one to three weeks before admission, five had been ill for three to six days, and the remainder (eight) had a history of symptoms for two days or less. One striking feature

was noted; all the 15 cases under six months of age were artificially fed, so that nutrition and lack of immune response to infection may be factors worthy of consideration. It was also noticed that of the 28 infants under six months of age who did not respond to treatment in hospital no fewer than 24 were artificially fed. Thus 90% of infants under six months old succumbing to infection were artificially fed. The histories of two cases typical of this group are summarized.

Case Reports

Case 1. B.A.M., aged 3 weeks, with a birth weight of 6 lb. 2 oz. had a 'cold in nose' for five days. The infant took feeds well up to four days before admission, then began to refuse feeds. He was constipated for three days, but there was no vomiting, and no cough.

Examination on admission showed the general condition to be very poor, and the infant in a collapsed state with subnormal temperature, pulse 144, respiration 40. No abnormal signs were found in the lungs.

At necropsy there was consolidation of the upper and lower lobes on the left side, even more marked on the right side, but no other pathological findings.

Case 2. S.B., aged 3 months, of birth weight 6 lb. 12 oz., had been breast fed for one week only.

The infant had been ill for two weeks with vomiting and failure to gain weight. The vomiting, projectile in type, increased during the past week, and the bowels were constipated.

Examination on admission showed a moribund, dehydrated baby, with cyanosis of hands and feet, and practically no respiration. Heart sounds were very faint.

Necropsy showed a wasted infant, whose lungs were congested with oedema and consolidation in posterior parts of both lungs. There were no other pathological findings.

No definite diagnosis had been made in any of these children and no specific treatment had been given. The presenting symptoms in ten of these cases were refusal of feeds, vomiting, and diarrhoea. In four other cases convulsions were the first symptom. Thus attention was not directed to a disease of the respiratory system and this may account for the delay in instituting therapy. It is therefore important to bear in mind that the signs of parenteral gastroenteritis may completely obscure the primary infection; to avoid such catastrophes as those recorded, the lungs must always be considered as the possible primary site.

In recent years it has been reported that massive single dose therapy with sulphonamides has been highly effective in the treatment of pneumonia in infancy and childhood (Platt, 1940; Vollmer, Abler, and Rosenberg, 1944; Hesselman, 1947). This provides a short, convenient, and satisfactory method of treatment which can be carried out in the home by the family doctor. In cases in which the diagnosis is not obvious, but where the possibility of pneumonia should be considered, this method will initiate the correct treatment although an early transfer to hospital and x-ray examination may be necessary to establish the localization of the infection. Considering the low toxicity of penicillin it may even be advisable to give a single massive injection of this drug in cases of doubt, such as those presenting with gastroenteritis or convulsions as the initial manifestation of bacterial invasion of the lungs, if by this means we can reduce the number of those infants who quickly succumb to the infection. Single massive dose treatment by the oral route with one of the sulphonamides or penicillin, which in infants under six months of age is readily absorbed from the alimentary tract, may commend itself because of the ease of administration; but the presence of vomiting so commonly encountered in these cases may render the method ineffective. The danger is that valuable time may be lost if only part of the chemotherapeutic dose is retained and proves inadequate to achieve a bacteriostatic level in the blood. A similar objection may be raised against the oral use of aureomycin, which has proved a valuable antibiotic in the treatment of bacterial and virus pneumonia of infancy and childhood (Olshaker *et al.*, 1949). However, because of its wider range of attack (which includes *Haemophilus influenzae* as well as pneumococci, streptococci, and staphylococci) and almost complete absence of toxicity, aureomycin may in future prove to be the drug of choice. Olshaker *et al.* reported 30 cases of bacterial pneumonia, including pneumococcal, streptococcal, and staphylococcal, as well as nine cases of atypical pneumonia; gratifying results were obtained in all but two cases. Aureomycin proved far less effective when given intramuscularly.

It has been generally accepted that white cell counts under 10,000 per c.mm. or over 50,000 per c.mm. are of serious prognostic significance. An analysis of white cell counts in this series reveals that no such prognostic importance can be attributed to a low total leucocyte count (Table 5). Of 23 infants with a count under 10,000 per c.mm. four died, while out of a total of 30 children with a white cell count of between 10,000 and 15,000 c.mm., six died. Furthermore it was found that the percentage of polymorphonuclear cells could not be used as an index of the severity of the disease. The number of polymorphonuclears varied from 20% to 80%, but there were approximately as many deaths recorded with polymorphonuclear percentages under 60 as above this level. Meyer (1931) attributed much more prognostic significance to the leucocyte count,

TABLE 5

LEUCOCYTE COUNTS IN 80 INFANTS UNDER TWO YEARS OF AGE

Age	5,000–10,000 per c.mm.		10,000–15,000 per c.mm.		15,000–20,000 per c.mm.		20,000–50,000 per c.mm.		Total	
	Recovered	Death	Recovered	Death	Recovered	Death	Recovered	Death	Recovered	Death
Under 6 months	12	3	11	5	8	2	2	3	33	13
6–12 months	3	1	5	1	7	1	1	1	16	4
1–2 years	4	0	8	0	1	0	1	0	14	0
Total	19	4	24	6	16	3	4	4	63	17

saying that it was inversely proportional to the mortality in 100 cases of pneumonia in infancy and childhood. Fleming (1936) similarly considered the leucocyte count of value in prognosis as a result of his study in adult pneumonia. In a study of the leucocyte count in croupous pneumonia in adults, von Wyss (1910) pointed out that leucopenia in itself is not a serious prognostic sign. It may be that improved methods of treatment now available for pneumonia have deprived the leucocyte count of its value in prognosis.

Summary

Two hundred and fourteen cases of pneumonia in infancy and childhood treated during 1946, 1947, and 1948 in two Manchester children's hospitals are reviewed.

The results of treatment with sulphonamides, penicillin, and combined sulphonamide and penicillin are compared.

The highest mortality occurred in infants under six months of age and combined therapy did not seem to affect the prognosis in this age group. There was a steep fall in the mortality rate for infants over six months but under one year of age, and a very low death rate for older children.

Attempts to lower the general mortality from pneumonia must be directed towards the treatment during the first six months of life.

Twenty cases died within 24 hours of admission to hospital. Reasons for the delay in diagnosis are discussed.

Leucocyte counts in 80 infants under two years of age are given. No prognostic significance can be attributed to the total white count or to the percentage number of polymorphonuclears.

Our thanks are due to Professor Gaisford for his encouragement and advice; to the physicians of the Royal Manchester Children's Hospital and the Duchess of York Hospital for permission to use their case records, and to the Medical Officer of Health for the mortality figures for Manchester.

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HEPATITIS ASSOCIATED WITH INFANTILE DIARRHOEA

BY

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Clinically, enlargement of the liver, jaundice and haemorrhages are well known complications occurring with infantile diarrhoea. But the pathological changes in the liver are not well defined. In a recent paper (Schlesinger, Payne, and Burnard, 1949) state that the histological changes have not been constant and do not fall into any well-defined groups. They found fatty infiltration, dilatation of the sinusoids, parenchymal degeneration, cellular necrosis, and cell infiltration with early fibrosis in some cases. Others have described changes varying from moderate periportal fatty degeneration to generalized fatty change with cellular necrosis (Blacklock, Guthrie, and Macpherson, 1937; Bray, 1945; Christensen and Biering-Soerensen, 1946; Giles, 1948). In addition to fatty change, Sakula (1943) noted in some cases an ' early proliferation of bile canaliculi as seen in adult cirrhosis ' and that 'these changes were most conspicuous in the jaundiced livers'.

Most cases of infantile diarrhoea show no pathological evidence of gastro-enteritis, and one is uncertain not only of the basic pathology of the condition, but even whether one is dealing with a single entity or a group of conditions. The number of cases showing acute ulcerative enteritis is small, but the following 15 cases have been collected from 350 consecutive necropsies at the Duchess of York Hospital for Babies, Manchester, and have been divided into two groups, those with jaundice and those without (Table 1). Thus five of 15 cases with an acute ulcerative enteritis show a form of hepatitis, and this is more common in the jaundiced cases in which the most severe liver damage might be

Table 1

Incidence of Hepatitis in Cases of Acute Ulcerative Enteritis

Group	No. of Cases	Pathological Changes in the Liver					
		' Hepatitis '	Capillary Biliary Thrombi	Fatty Infiltration	Atrophy	Foci of Erythro-poiesis	No change
Cases with jaundice ..	8	4	3	0	0	1	0
Cases without jaundice	7	1	0	2	1	0	3

Table 2

Incidence of Hepatitis in all Cases of Infants Dying with Jaundice

Cases with Infantile Diarrhoea and other Febrile Conditions	No. of Cases	Other Pathology	No. of Cases
' Hepatitis '	11	Rh. iso-immunization	6
		Congenital biliary cirrhosis	3
Biliary thrombi	3	Congenital syphilis	1
		Congenital tuberculosis	1
Fatty infiltration	1	Giant cell hepatitis	1
		Massive hepatic necrosis	2
Total	15		14

expected. If we now consider all the cases of infants dying with jaundice (excluding physiological icterus) in this series of necropsies, we find that hepatitis is the most common finding associated with jaundice in infancy.

The group of cases with infantile diarrhoea will be considered in detail (Table 2). Material from the liver, pancreas, umbilicus, and other organs was available for examination in most cases. Special attention was paid to the umbilical vessels since infection can lead to liver changes (Morison, 1944); to the pancreas, in view of the cirrhosis described in association with cystic fibrosis of the pancreas (Farber, 1944); and to the bile passages, since 'ascending infection' of the bile ducts is often considered to be the cause of jaundice. Frozen sections were stained by sudan IV for fat. Paraffin sections were stained by haemalum and eosin, Weigert's haematoxylin and van Giesen, Lillie Gram stain, and Gomori's reticulin silver impregnation technique. Most of the necropsies were on infants under one year, the average age being about two months.

Group 1 consisted of cases of acute hepatitis with bile duct proliferation. Under A are studied cases with severe jaundice and marked histological changes in the liver (Table 3).

Clinical Summaries (Group A.)

Case 1. The infant developed diarrhoea and vomiting eight days following mastoidectomy and jaundice appeared after seven days. The jaundice deepened and he became comatose and died seven days later.

Case 2. The stools became pale and offensive six days before admission, and four days later the infant developed diarrhoea and vomiting. Bruising of the abdominal wall appeared and he died 24 hours later.

Case 3. Jaundice was first noticed two days before admission and since then there had been diarrhoea and vomiting. The infant died three days later.

Case 4. A premature infant, who developed attacks of cyanosis at two weeks, following admission to hospital, developed diarrhoea and vomiting which persisted for 11 days. He became jaundiced and emaciated.

Naked Eye Appearance of the Liver

In each case the liver was enlarged, green or greenish-yellow, and showed marked centrilobular congestion. The capsule was smooth and there was no distortion of the pattern.

Histological Features

In cases 1, 2, and 3 the liver showed a severe periportal fatty infiltration (Fig. 1) but in case 4 there was no fat present, and the cells were shrunken and the sinusoids dilated. There was necrosis of

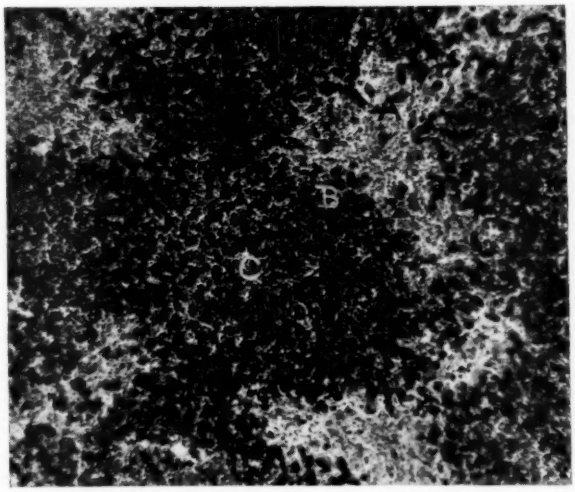

FIG. 1.—Case 1. Liver showing marked periportal fat infiltration. A, widened portal tracts. B, periportal zone. C, centre lobule. Fat appears black. Sudan IV. × 60.

TABLE 3

CASES OF HEPATITIS WITH SEVERE JAUNDICE

Case	Age	Sex	W.B.C.	Duration Jaundice (Days)	Alimentary Tract	Other Pathology
1	9 months	M.	16,000 P.65%	7	Acute enteritis with pneumatosis	Recent mastoidectomy.
2	6 weeks	M.	25,600 P.85%	7	No inflammation	Impervious cystic duct. Bronchopneumonia.
3	3 weeks	F.	17,600 P.70%	5	No inflammation	Acute pancreatitis. Bronchopneumonia.
4	6 weeks	M.		7	Acute enterocolitis with 'pneumatosis'	Splenomegaly with fibrinous perisplenitis.

P = Polymorphonuclear leucocytes.

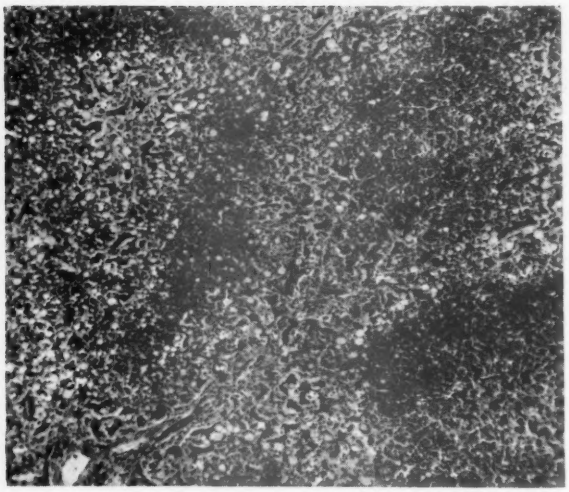

FIG. 2.—Case 1. Liver showing proliferation of bile canaliculi around the portal tracts, with centrilobular congestion. H.E. × 60.

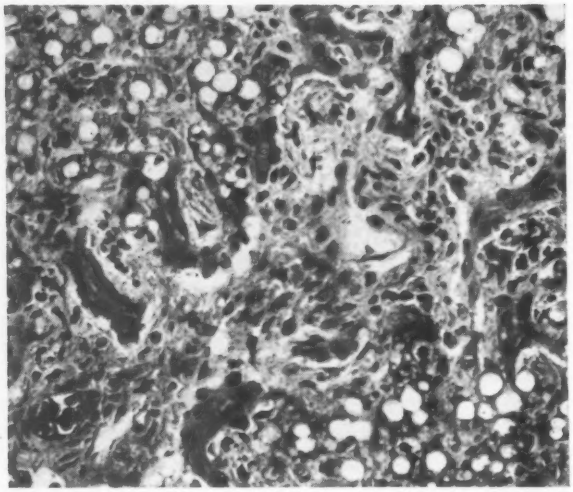

FIG. 3.—Case 2. Liver showing proliferating bile canaliculi, inflammatory cells and fatty infiltration. H.E. × 220.

parenchymal cells in the periportal zone of the lobule with a scattered infiltration of mononuclears and polymorphs. The most striking feature was the proliferation of bile canaliculi in this zone, frequently involving half the lobule (Figs. 2 and 3). Mitoses were present in cells of these bile canaliculi. There was also proliferation of fibroblasts, and in case 1 sections stained by van Giesen showed an increase of pink staining fibres. There was marked centrilobular congestion with varying degrees of centrilobular necrosis. The intercellular bile capillaries at the centre of the lobules were distended with bile. No organisms could be demonstrated. Case 3 showed microscopic evidence of an acute pancreatitis but there was no evidence of infection involving the bile ducts or the umbilicus vessels in any of the cases.

Under B cases with moderate jaundice and less severe histological changes in the liver were studied (Table 4).

TABLE 4
CASES OF HEPATITIS WITH MODERATE JAUNDICE

Case	Age	Sex	W.B.C. (c.mm.)	Duration Jaundice (Days)	Alimentary Tract	Other Pathology
5	4 weeks	M.	30,000 Protein 75%	2	Ulcerative enteritis	Haemorrhages on the pleura
6	3 weeks	M.	15,000 Protein 68%	12	No inflammation	Haemorrhages in the brain
7	3 weeks	M.	8,400 Protein 31%	2	No inflammation	—
8	10 months	F.	6,600 Protein 26%	1	No inflammation	Coeliac syndrome
9	10 weeks	F.	—	2	No inflammation	Acute meningitis. Streptococcal haemolytic septicaemia
10	4 weeks	F.	19,600 Protein 47%	4	Ulcerative enteritis	Haemorrhages in the meninges
11	3 weeks	F.	—		No inflammation	—

P=Polymorphonuclear leucocytes.

Clinical Summaries (Group B)

Case 5. The infant developed diarrhoea and vomiting following a Ramstedt operation and three days later became jaundiced. The following day he vomited blood-stained material, had severe melaena, and died.

Case 6. The infant had severe jaundice with a profuse aural discharge at ten days. The stools and urine were normal until seven days later when he developed diarrhoea and vomiting.

Case 7. Diarrhoea and vomiting began three days after admission, and five days later the infant became jaundiced and died the following day.

Case 8. This case presented as a coeliac syndrome and improved for three weeks, when the baby started diarrhoea and vomiting, developed slight icterus, and rapidly deteriorated.

Case 9. The illness began with convulsions and presented as meningitis. The baby was treated by chemotherapy and penicillin, but developed progressive jaundice.

Case 10. The infant had always been slow with feeds and the motions relaxed. Jaundice was noted the day before admission and she died three days later.

Case 11. The infant developed diarrhoea and vomiting and was jaundiced and moribund on admission.

Naked Eye Appearance of the Liver

In each case the liver was enlarged, bright yellow, or showing marked fatty change. The capsule was smooth and there was no distortion of the pattern.

Histological Features

The histological features were similar to those in Group A but less severe. All cases showed a periportal fat infiltration though this was very small in case 9. There was necrosis of parenchymal cells in the periportal zone with an infiltration of mononuclears and lymphocytes. Proliferating bile canaliculi and fibroblasts were present but not involving so much of the lobule. No organisms were seen and there was no indication of infection of the bile ducts. In case 6, in which the jaundice had been prolonged, there was an increase in pink staining fibres with van Giesen stain around the portal tracts. Case 8 showed an intense fat infiltration of the whole lobule with many cells ballooned and frequently degenerating. This was associated with atrophy of the pancreatic acinar tissue.

Group 2 consisted of cases of infantile diarrhoea with jaundice not showing hepatitis.

There were three cases showing ulcerative enteritis with jaundice of one to six weeks' duration, in which the liver was enlarged and dark green. The essential histological feature was distension of the intercellular bile capillaries in the absence of an inflammatory reaction, fatty infiltration or swelling of the parenchymal cells, or obstruction of the bile ducts. The fourth case was an infant with fibrinous pericarditis and mild jaundice of two days' duration. The liver showed periportal fatty infiltration but no bile duct proliferation, inflammatory infiltration, or distension of the bile capillaries. The available data are not sufficient to determine the cause of the jaundice in these cases, but the histological findings in the liver suggest a non-hepatic origin.

Discussion

Of these 15 cases of jaundice associated with infective conditions 11 fall into the same group, the essential features of which are necrosis of parenchymal cells around the portal tracts with a proliferation of bile canaliculi and fibroblasts, and an infiltration of inflammatory cells. It is an acute process and, as shown by the severe cases in Group A, half the lobule can be replaced by proliferating bile canaliculi when jaundice has lasted seven days. Most cases show a marked periportal fatty infiltration, but the severity is variable, and in case 4 no fat was present in the liver. The liver was invariably enlarged and the colour was dark green when jaundice had lasted about seven days, and a bright yellow with a shorter duration. Sakula (1943) noted the proliferation of bile canaliculi, but it is surprising that this has not been commented upon by others. Giles (1948) reported on 55 necropsies, 13 showing jaundice, but did not remark on any proliferation of bile canaliculi. But one of his illustrations showing 'periportal distribution of fatty degeneration' shows structures which clearly resemble bile canaliculi.

Liver sections from 200 infants were examined to determine whether these histological features occurred without jaundice. In cases showing appreciable periportal fat infiltration the small bile ducts may appear more prominent owing to

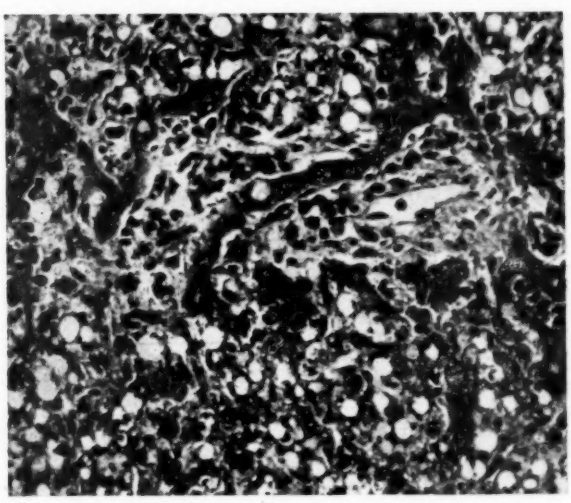

FIG. 4.—Cretin with ulcerative colitis, but no jaundice. Liver showing proliferating bile canaliculi, inflammatory cells and fatty infiltration. H.E. × 220.

vacuolation of the liver cells, but proliferation of bile canaliculi was found in only one case without jaundice (Fig. 4). This was a girl aged 4½ months, a cretin who developed otitis media and ulcerative enteritis (case included in Table 1). The intercellular bile capillaries were distended with bile suggesting that jaundice would have appeared had life been prolonged.

Most of the cases have a definite history of severe diarrhoea and vomiting with the development of an enlarged liver, jaundice, and occasionally haemorrhages, but in only four cases was there pathological evidence of acute entero-colitis, two of these also showing 'pneumatosis' of the bowel wall. In case 2 jaundice appeared to precede the diarrhoea and vomiting, but histories of young infants are not always reliable. In case 6 jaundice was at first associated with otitis media, while case 9 presented with meningitis and septicaemia and no history of diarrhoea. Thus, although this form of hepatitis apparently can occur with other infective conditions, it is most commonly associated with infantile diarrhoea.

Fat infiltration of the liver is the most constant change which has been described in association with infantile diarrhoea. It can be caused experimentally by various poisons such as phosphorus and chloroform, and also by dietary deficiency. Fat infiltration of the liver also occurs in fasting animals (Mottram, 1909; Dible, 1932). In the mouse, fat infiltration is marked after 24 hours' starvation, but by the third and fourth days, when all available carcase lipids have been mobilized, the liver contains no stainable fat (Hodge, McLachlan, Bloor, Stoneburg, Oleson, and Whitehead, 1941). Thus in the fasting mouse fatty infiltration of the liver is a physiological process and is not an indication of serious liver damage. Fat infiltration is much more common in infants than in adults, being found in about 50% of necropsies (65 of 135 livers in this series). It appears to be related to the nutritional state of the infant, being scanty with emaciation. This high incidence in infancy may be related to the high metabolic rate. Thus the fat infiltration associated with infantile diarrhoea may be toxic or may be a physiological reaction to starvation. It is not possible to evaluate the relative importance of these factors. The absence of fat in the liver in case 4, where there is marked proliferation of bile canaliculi, suggests that fat infiltration and necrosis of the liver cells are not dependent processes.

It is known that necrosis of liver parenchymal cells may be caused either by deficiency of factors essential to cellular activity, or by a toxic process (Himsworth, 1947). Deficiency necrosis is commonly of massive type, although this mechanism is believed to operate in centrilobular necrosis where some toxin, as with CCl_4 or infective hepatitis, causes swelling of the peripheral cells with obstruction of the intralobular circulation. Other poisons, such as allyl formate (Himsworth, 1947), especially when given by intraperitoneal injection, produce a peripheral zonal necrosis. If repeated small doses of allyl formate are given to a rat or rabbit, then proliferation of bile canaliculi occurs around the portal tracts (Figs. 5 and 6), comparable to that

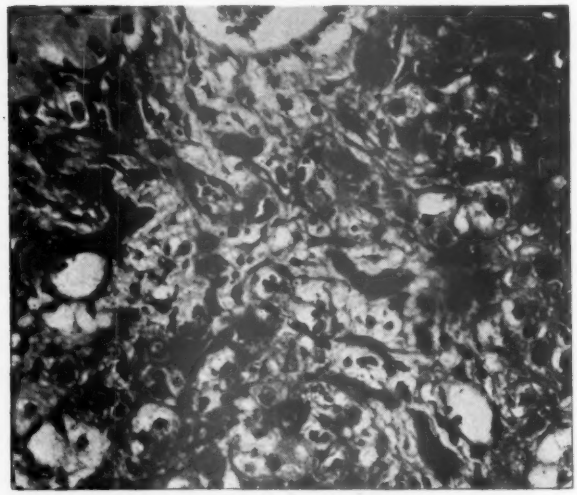

FIG. 5.—Rat liver. Allyl formate. Proliferation bile canaliculi and cell necrosis around portal tract seven days after initial dose. (·015 ml. alternate days, 3 doses.) H.E. × 220.

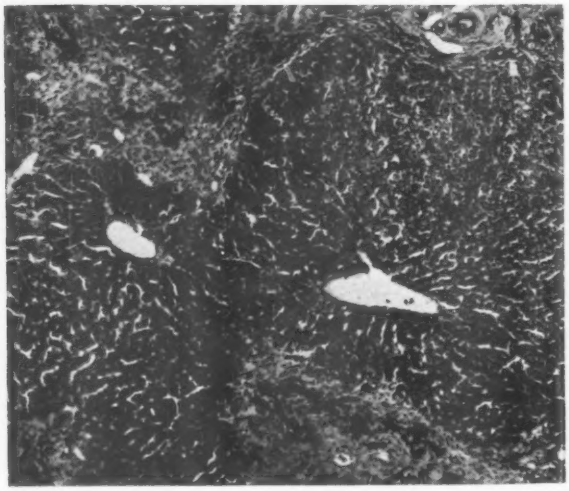

FIG. 6.—Rabbit liver. Allyl formate. Fibrosis and proliferation bile canaliculi around portal tracts with normal central veins. Thirteen days after initial dose. (0·1 ml. first and fifth days.) H.E. × 60.

found in these cases of hepatitis. We do not see the same extensive peripheral zonal necrosis in hepatitis in infants, but this can be explained by the slower access of toxin to the liver. Proliferation of bile canaliculi appears to follow any liver cell necrosis in which rapid regeneration of the liver cells does not occur. It seems probable that they are formed by a proliferation of cells (as evidenced by mitoses) from the bile ducts, which then grow along the intercellular bile capillaries in an endeavour to form functional continuity with the remaining viable liver cells.

The histological features of this form of hepatitis somewhat resemble subacute cholangio-hepatitis in the adult, where proliferation of bile canaliculi and fibroblasts follows an inflammatory necrosis of cells around the portal tracts (Himsworth, 1947). Cholangio-hepatitis is commonly associated with obstruction of the bile ducts and the primary lesion is cholangitis. In these infants there is no obstructive lesion and the absence of an inflammatory process involving the bile ducts and the rarity of inflammatory lesions in the duodenum is clear evidence that the process does not arise as cholangitis.

This form of hepatitis is quite distinct histologically from the interstitial hepatitis described by Morison (1944) and Lesage and Demelin (1898) in cases with umbilical infection. It also differs from the lesion in infective jaundice of intestinal origin described by Lesage and Demelin (1898), which appeared to be a massive hepatic necrosis. It is distinct from infective hepatitis, where centrilobular necrosis is the salient feature and bile duct proliferation is not found unless massive necrosis occurs (Himsworth, 1947). The regularity of the lesion and the periportal distribution distinguish it clearly from subacute hepatic necrosis which is now recognized to be the lesion in ' biliary cirrhosis ' of Hindu infants (Himsworth, 1947).

Case 8 differed from the others in that the hepatic lesion was associated with atrophy of pancreatic acinar tissue, and the fat infiltration was diffuse and severe. Prolonged fatty infiltration due to dietary deficiency may lead to a diffuse hepatic fibrosis involving both the portal tracts and central veins (Himsworth, 1947). But the histology in case 8 bears no resemblance to diffuse hepatic fibrosis and is definitely an acute process localized to the periportal zone. Nor does it resemble the groups of dilated ducts containing eosinophilic material described by Farber (1944) in the liver in cystic fibrosis of the pancreas.

This form of hepatitis appears to be limited largely to infancy when it is apparently a common cause of fatal jaundice. Himsworth (1947) discusses experimental peripheral zonal necrosis but does not give any examples in human pathology. It is possible that the liver cells in infancy are more easily damaged than in adult life. The histological picture with periportal bile duct proliferation might be termed a ' biliary cirrhosis,' although in most cases there has been insufficient time for fibrosis to occur, and the problem arises as to whether there is any relation between the aetiology of this form of hepatitis and congenital biliary cirrhosis. It is generally assumed that the latter is of obstructive origin, but many cases occur in the absence of atresia of the bile ducts. As originally suggested by Rolleston and McNee (1929), some intra-uterine toxin may produce a periportal necrosis of liver cells, and the frequent occurrence of this reaction in infancy adds support to this hypothesis.

Summary

A form of hepatitis associated with jaundice and infantile diarrhoea is described. The main features are a periportal necrosis of parenchymal cells, with an infiltration of inflammatory cells, and a proliferation of bile canaliculi and fibroblasts. Most cases show fatty infiltration.

The aetiology is discussed and it is considered that the hepatitis is caused by a toxin reaching the liver by the blood stream.

A possible relationship between this form of hepatitis and congenital biliary cirrhosis is suggested.

I wish to thank the honorary staff of the Duchess of York Hospital for Babies, Manchester, for the clinical notes, Professor S. L. Baker for helpful advice, and Mr. F. Ward for the photomicrographs.

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EXCRETION AND INTAKE OF B VITAMINS IN NEWBORN INFANTS

BY

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The present work was undertaken in an attempt to throw more light on the metabolism of vitamin B in the newborn infant, and, in particular, by means of balance experiments, to seek evidence of the biosynthesis of B vitamins in the intestinal tract during the first week after birth. The investigations were confined to aneurin, riboflavin, and nicotinic acid and its metabolites.

Very little work has been done on this subject in the past and balance studies have not been attempted. Neuweiler (1943) estimated the urinary excretion of aneurin by infants one to ten days old and observed that the values were low, but higher during the first four or five days than later. Coulson and Stewart (1946) studied the ability of infants to methylate nicotinamide and, in the course of this work, estimated the normal urinary output of N-methylnicotinamide on the first day after birth. They reported an average urinary output of 3·2 mg. of N-methylnicotinamide per 24 hours. Hamil, Coryell, Roderuck, Kaucher, Moyer, Harris, and Williams (1947) examined the concentrations of aneurin, riboflavin, nicotinic acid, N-methylnicotinamide, pantothenic acid, and biotin in the urine of infants during the first week after birth. In the main their results are confirmed by the present findings in so far as the urinary concentrations of aneurin, riboflavin, and nicotinic acid and its metabolites are concerned, but they did not study the faecal concentration and output or attempt to relate the total output to the intake. Their values for the maximum concentration of aneurin in the urine were lower than those found by Neuweiler (1943) and in the present investigation; they also found somewhat lower concentrations of N-methylnicotinamide than are now reported. Their work came to our attention after our experiments had been completed.

Material and Methods

Urine and faeces were collected from male children, born in the 77th British General Military Hospital, Wuppertal, and in the Landesfrauenklinik, Wuppertal. The mothers and the children themselves were, as far as could be ascertained, normal. The children were all full-term, delivery was without special event, and the birth weights were all between 2,750 and 3,500 g.

Urine passed during delivery or immediately after was collected whenever possible in a test-tube. Thereafter the urine was collected by means of a glass apparatus which enclosed the penis and scrotum and was held in place by loops of elastic fastened to an elastic belt round the child's waist. The distal end of the apparatus was narrow and had a rubber tube attached to it. This led normally into a dark glass collecting-bottle containing acetic acid and toluene that stood outside the cot. When the child went to the breast, however, the tube was clipped off near its end, and urine passed during feeding time collected in the apparatus and tube and was drained off into the bottle when the child returned to its cot. The children were not bathed during the experimental periods, but were washed without being immersed.

Meconium and faeces were caught in mackintosh squares inside the usual napkins, and this method was found to be satisfactory for all except the most liquid faeces. Rather surprisingly, the use of the mackintosh for several days on end did not cause any skin trouble, possibly because urine did not come into contact with the skin. Meconium or faeces adhering to the skin was removed with a spatula. The faeces were collected every four hours and were stirred up as soon as possible with a few drops of hydrochloric acid and toluene. They were kept in porcelain or dark glass containers.

At both the hospitals where this work was done it was the practice to give no fluid by mouth in the first 36 hours after birth, unless the child was obviously thirsty; he was then given 15 to 20 ml. of water sweetened with sugar. After about 36 hours the child was put to the breast. Of the children used for the investigation, all except one were wholly breast fed during the period covered by the collections.

Samples of milk were obtained by expression. They were not acidified, but were placed immediately in a refrigerator and analysed as soon as possible. Urines were protected throughout against daylight, which would have destroyed riboflavin, and were also analysed without delay. The faecal specimens were kept in a refrigerator until they could be analysed.

Aneurin was estimated by a modification of the thiochrome method similar to that described by Greenberg and Rinehart (1945). Each sample of food and faeces was extracted with a 0·65 % solution of HPO_3, and the extract was incubated with takadiastase to convert cocarboxylase to the free vitamin. Urine was not treated with takadiastase. The extract, or the diluted sample of urine, was passed through a column containing 2 g. 'decalso,' and the adsorbed aneurin was eluted with a 25% solution of KCl containing sufficient HCl to bring the normality to 0·1. The aneurin in the eluate was oxidized to thiochrome by means of alkaline ferricyanide under rigidly controlled conditions. For the blank the ferricyanide was omitted. An internal standard was included in each determination by adding a known amount of aneurin to a portion of the extract or diluted urine before adsorption, and carrying out a second analysis on this solution. Under these conditions a linear relationship was obtained between the galvanometer reading and the amount of aneurin present in the sample.

As Najjar and Ketron (1944) have pointed out, the thiochrome method gives erroneous results when N-methylnicotinamide is present, for example in the estimation of aneurin in urine. However, since the error varies directly with the amount of N-methylnicotinamide present, and since N-methylnicotinamide was estimated in every sample which contained this compound, it was possible to apply a correction. The correction used, which was determined by experiment, was as follows:

Corrected aneurin concentration (μg./g.)=uncorrected aneurin concentration (μg./g.)—0·009 × N-methylnicotinamide concentration (μg./g.).

Riboflavin was estimated by the method of Slater and Morell (1946), using an artificial source of ultra-violet light instead of sunlight for the destruction of riboflavin in the pyridine-butanol extracts. The tubes containing the extracts were placed in a circular rack which could be made to rotate slowly, by means of an electric motor, around an ultra-violet lamp. In this way all extracts received the same amount of irradiation. Riboflavin was extracted from all samples of foods and faeces by autoclaving in 0·25 *N* H_2SO_4 solution for 35 minutes at 120° C. An internal standard was included in each determination in the manner described by Slater and Morell. The relationship between the galvanometer deflection and the amount of riboflavin present was linear.

Nicotinic acid was estimated in foods and faeces by the method of Dann and Handler (1941). Nicotinic acid and its acid-hydrolysable derivatives in urine were estimated by the method of Perlzweig, Levy, and Sarett (1940); in this method concentrated hydrochloric acid is used for the hydrolysis. N-methylnicotinamide was estimated by the method of Huff and Perlzweig (1947). Since this method was worked out only for urine, an attempt was made to confirm the results obtained for faeces by another method. The colorimetric method of Sarett (1943) for total derivatives of N-methylnicotinic acid was tried, but accurate results could not be obtained, since the colouring matter in the extracts was not entirely removed by the preliminary absorption treatment. A red colour was, however, produced after the addition of benzidine, thus indicating that N-methylnicotinamide was present, and confirming, to some extent, the results obtained by the method of Huff and Perlzweig.

Results

Urinary Concentrations and Output. Before the balance experiments were started a preliminary study was made of the levels of urinary excretion of the vitamins on each successive day during the first week after birth. Some of the results are given in Table 1. Total N was also estimated in the urine of one infant. The length of the first period was in every case less

TABLE 1

URINARY EXCRETION OF B VITAMINS AND TOTAL N BY INFANTS IN THE FIRST WEEK AFTER BIRTH

Day	Infant No. 1					Infant No. 2		Infant No. 3	
	Aneurin		N-methylnicotinamide		Output Total N (mg.)	Riboflavin		Riboflavin	
	Concentration (μg./ml.)	Output (μg.)	Concentration (μg./ml.)	Output (μg.)		Concentration (μg./ml.)	Output (μg.)	Concentration (μg./ml.)	Output (μg.)
1	0·17	3(a)	45	769(a)	44(a)	0·23	4(b)	—	—
2	0·70	5	82	621	31	0·31	6	1·50	15(c)
3	0·83	29	89	3,104	247	0·49	9	0·38	4
4	0·57	3	72	430	24	0·09	7	0·03	0·2
5	0·20	6	23	652	52	0·04	5	0·29	3
6	0·19	19	17	1,623	205	0·04	4	0·14	16
7	0·14	4	12	355	77	—	—	—	—
8	—	—	11	698	95	—	—	—	—

(a) 0–14 hours after birth.
(b) 0–20 hours after birth.
(c) Collection began 17 hours after birth.

than a full day but the later periods were always 24 hours long.

Perhaps the most striking feature of the results is the relatively large amount of N-methylnicotinamide which is apparently excreted by the newborn child. This phenomenon was not especially commented on by Coulson and Stewart (1946) but was discussed by Hamil *et al.* (1947). As a confirmatory measure, the N-methylnicotinamide in the urine produced by an infant on the first day after birth was estimated by the method of Sarett (1943) as well as by that of Huff and Perlzweig. The two results were almost identical; one indicated an excretion of 3,136 μg. per day and the other 3,065 μg. per day.

The concentrations of aneurin, riboflavin, and N-methylnicotinamide in the urine tended to be much higher on the first three or four days after birth than subsequently, and the maximum concentrations occurred on the second or third day. These results confirm the findings of Neuweiler (1943) and of Hamil *et al.* The alterations in concentration followed a regular pattern and were probably due, to a large extent, to alterations in water balance. The total daily excretions were much more irregular and for this there may have been several reasons. The simplest would be that the collections were incomplete. The supervision of the infants was, however, so close that it is unlikely that enough urine was lost to affect the results appreciably. It was more probable that the amounts of urine which were collected had been formed over periods whose length could not be exactly determined, because the bladder was not always completely emptied when the infants passed urine spontaneously. The most likely reason is that there is an inherent irregularity in the metabolism of the newborn infant. The total output of N was also irregular, presumably for the same reasons: similar irregularities in the N excretion of infants have been observed by other workers (Reusing, 1895; Birk, 1912; Thomson, 1944; Barlow and McCance, 1948), and the question has been discussed by Barlow and McCance.

Hamil *et al.* reported a sharp falling-off in the excretion of the B vitamins towards the end of the first week. These authors did not, however, actually measure the daily urinary volumes of the infants they studied. Instead they took average values for urinary volume found by other investigators and used them for the calculation of the vitamin excretions.

Balance Experiments. The results of the two balance experiments are summarized in Tables 2, 3, and 4. Each period was a full 24 hours, the first starting at the time of birth. Both infants were fed by their mothers, but one of them (No. 5) received supplementary feeds of cow's milk and oat flour. These feeds were analysed, but the milk of the mother was so scanty that none could be obtained for analysis. The mother of infant No. 4 had plenty of milk, and results obtained by analysing a sample taken on the sixth day were used in calculating the B vitamin intakes of both children. This may have given values for the earlier days which were somewhat too high, because the concentration of B vitamins in the milk is greater at the end of the first week of lactation than at its beginning (Roderuck, Williams, and Macy, 1946; Roderuck, Coryell, Williams, and Macy, 1946).

In general, the data for the urinary excretions confirmed the results of the preliminary studies.

Aneurin. Meconium passed at birth by child No. 5 was analysed, but no aneurin was found; apparently none had entered the gut up to the time of birth, or it had been destroyed. Excretion by both children began on the day after birth (Table 2) and tended to rise towards the end of the week. Nevertheless, the balances were probably positive by the fourth or fifth day. The aneurin excreted

TABLE 2

ANEURIN BALANCES IN THE FIRST WEEK AFTER BIRTH

Day after Birth	Infant No. 4					Infant No. 5				
	Intake (μg.)	Output (μg.)			Balance	Intake (μg.)	Output (μg.)			Balance
		Urine	Faeces	Total			Urine	Faeces	Total	
1	0	13	2	15	Negative	0	—	7	—	Negative
2	9	—	11	—	Negative	7	—	11	—	Negative
3	26	17	19	36	Negative	34	—	2	—	Doubtful
4	37	22	57	79	Negative	40	6	14	20	Positive
5	48	21	—	—	Doubtful	52	9	25	34	Positive
6	37	3	26	29	Positive	65	10	19	29	Positive
7	37	11	—	—	Doubtful	75	5	50	55	Positive

may have been derived partly from desquamated cells and partly from food residues; it is possible that some had been produced by bacterial synthesis.

Riboflavin. The urine passed by child No. 4 at birth, and the urine and meconium passed then by child No. 5 contained small amounts of riboflavin (Table 3). On the first day both children excreted fairly large quantities of the vitamin, mostly in the meconium and faeces: in the next days the excretion tended to fall, and by the end of the week the two balances were positive. The results suggest the rapid exhaustion of a store in the gut derived from amniotic fluid, cells, or secretions, and although it is possible that by the end of the week some synthesis had begun, the more likely source of the riboflavin which was excreted was the food.

Nicotinic Acid and its Metabolites. The meconium passed at birth by child No. 5 contained considerable amounts of N-methylnicotinamide (Table 4), and in the next days large quantities of this metabolite were excreted, most of it in the urine. The balances were almost certainly negative all the week, but became less so towards the end.* No conclusions can be drawn from the values for the excretion of nicotinic acid by the children. The high figures for the urinary excretion of N-methylnicotinamide may be partly explained by the finding (Dean and Holman, 1949) that newborn infants excrete on an average only about one-third as much N-methyl-2-pyridone-5-carboxylamide as N-methylnicotinamide, whereas adults excrete almost twice as much. It was

* In the calculation of the intake of nicotinic acid, no allowance was made for amounts which might have been derived from tryptophane. Evidence has recently been produced that the acid can be formed in this way by children aged 3 to 24 months (Snyderman, Ketron, Carretero, and Holt, (1949) and by adults (Holman and de Lange, 1950). The ability of the newborn infant to effect the conversion obviously needs investigation.

TABLE 3
RIBOFLAVIN BALANCES IN THE FIRST WEEK AFTER BIRTH

Day after Birth	Infant No. 4					Infant No. 5				
	Intake	Output (μg.)			Balance	Intake	Output (μg.)			Balance
		Urine	Faeces	Total			Urine	Faeces	Total	
At birth		1	—	—			1	8	9	
1	0	29	47	76	Negative	0	17	68	85	Negative
2	26	12	110	122	Negative	19	8	40	48	Negative
3	72	7	48	55	Positive	71	—	10	—	Positive
4	103	4	38	42	Positive	86	8	20	28	Positive
5	134	2	—	—	Positive	111	20	29	49	Positive
6	106	0·2	19	19	Positive	136	12	12	24	Positive
7	106	3	—	—	Positive	157	6	41	47	Positive

TABLE 4
NICOTINIC ACID BALANCES IN THE FIRST WEEK AFTER BIRTH

Day	Infant No. 4					Infant No. 5				
	Intake of Nicotinic Acid	Output			Balance	Intake of Nicotinic Acid	Output			Balance
	(μg.)	N-methyl-nicotinamide*		Nicotinic Acid		(μg.)	N-methyl-nicotinamide*		Nicotinic Acid	
		Urine (μg.)	Faeces (μg.)	Urine (μg.)			Urine (μg.)	Faeces (μg.)	Faeces (μg.)	
At birth		—	—	—			71	106	—	
1	0	2,759	113	77	Negative	0	1,587	1,006	211	Negative
2	121	939	230	30	Negative	88	241	289	230	Negative
3	330	1,756	196	42	Negative	462	310	25	—	Doubtful
4	473	2,920	153	47	Negative	544	818	162	142	Negative
5	616	1,927	—	45	Negative	707	1,393	42	162	Negative
6	484	182	43	19	Doubtful	870	1,271	17	—	Negative
7	484	1,111	—	68	Negative	1,006	339	121	236	Doubtful

* Expressed as nicotinic acid.

suggested that the difference could be accounted for by a lower level of enzyme activity in the infant. The method used for the estimation of the N-methylnicotinamide is probably not specific for this substance; other substances such as coenzymes are almost certainly estimated and they also may be excreted in relatively large amounts by the child.

Little is known about the nicotinic acid metabolism of the human foetus and of the newborn infant. However, it has been established (Dean and Holman, 1948) that the concentrations of nicotinic acid in the blood of the mother and child at birth are approximately equal, and it seems unlikely from this and other evidence (Lwoff, Morel, and Digonnet, 1941) that the child at birth possesses any large store of the acid. In an attempt to throw further light on the question, amniotic fluid was analysed for N-methylnicotinamide, the method of Huff and Perlzweig (1947) being used. The results indicated the presence of amounts of the order of 0·6 to 1·4 μg./ml., but owing to the unusually high 'blank' fluorescence, the concentrations cannot be stated with certainty. These amounts may originate entirely as the result of urinary excretion into the amniotic fluid by the foetus, and this fluid, swallowed by the infant before birth, may provide some of the vitamin found in the meconium and the first faeces. Small amounts may be derived from intestinal secretions or desquamated cells, but it is extremely unlikely that micro-organisms capable of synthesizing the vitamin are present in the gut before birth. The fall in the output after birth suggests an exhaustion of the original supply, and very little synthesis by intestinal organisms in the first few days of life. The possibility that a part of the faecal N-methylnicotinamide was derived from unaltered food residues was eliminated by analysing a sample of human milk for N-methylnicotinamide by the method of Huff and Perlzweig (1947). No detectable amount was present.

Discussion

Although our results may have contributed towards the definition of the status of the newborn child in regard to some of the B vitamins, they do not provide clear evidence of synthesis in the gut. For that purpose methods are needed which will serve to differentiate between amounts of the vitamins acquired during intra-uterine life and others derived from bacterial action or from food residues. It seems unlikely, on the basis of the present evidence, that synthesis of any of the three vitamins studied occurs in appreciable quantities before the end of the first week.

Summary

The excretion and intake of aneurin, riboflavin, nicotinic acid and its derivatives have been studied in newborn infants. After preliminary studies of urinary excretion balance experiments were conducted on two infants.

The aneurin and riboflavin balances were probably negative for about four days, and then became positive.

The nicotinic acid balance remained negative until the end of the first week, largely because of the extremely high excretion of N-methylnicotinamide. This high excretion may be due to the fact that infants, unlike adults, appear to produce in their urine much less N-methyl-2-pyridone -5-carboxylamide than N-methylnicotinamide.

No clear evidence of bacterial synthesis of B vitamins was obtained.

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LEAD POISONING IN INFANCY

BY

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Lead poisoning in infancy and childhood is a well-recognized and apparently common condition in America. In Holt's 'Diseases of Infancy and Childhood' (1940) it is stated that 'lead poisoning is one of the common and most serious forms of intoxication recognized in childhood.' Byers and Lord (1943) reviewing the records of the Children's Hospital, Boston, found 128 cases of this condition during a ten year period. During the last 15 years a large number of papers on this subject have appeared in the American journals, many of them reporting a series of cases. In Great Britain, on the other hand, lead poisoning appears to be comparatively rare, or at least rarely recognized, in the early years of life, if the infrequency of published reports may be taken as a sound guide. Gordon and Whitehead (1949) have recently reported one case in an infant aged 6 months, Findlay (1935) reported one case in an infant of 3 months, and Rodgers, Peck, and Jupe (1934) one case in a child aged 2 years. The *Index Medicus* contains no record of any other papers on this subject in the British literature during the past 15 years.

The following report of a case of lead encephalopathy in a young infant may therefore be of some interest, and serve to draw attention to the diagnosis of a condition which may well be missed unless the possibility of its occurrence is constantly borne in mind.

Case Report

A boy aged 4 months was admitted to the Royal Aberdeen Hospital for Sick Children on July 19, 1947, on account of convulsions. He had been breast fed and had always appeared very well until two weeks before admission when his mother decided to discontinue breast feeding and changed his feeds to a full cream dried milk. From this time he became listless and began to vomit occasionally after and during feeds. He had no bowel upset and did not appear to have any abdominal pain. On the morning of admission he had a right-sided convulsion with muscular twitching persisting for half an hour, succeeded by temporary paralysis of the right arm and leg.

The infant was the first child of healthy parents and was born prematurely after a normal labour, his birth weight being 5 lb. Neither parent had complained of any symptoms suggestive of lead poisoning.

When examined on admission he was seen to be a pale infant in good general condition. The fontanelle was tense and there was a right facial paresis. No other abnormality was perceived.

During the first two days the facial paresis cleared up but convulsions recurred intermittently in spite of repeated large doses of chloral. For long periods there was muscular twitching involving at times the whole body and at times only the left side. After this the fits ceased spontaneously and did not recur, except for one brief, right-sided fit on the eighth day after admission. He took feeds well, did not vomit, and remained in good general condition.

Investigations. Routine urine examination was negative. Lumbar puncture on admission produced clear cerebrospinal fluid under normal tension: the fluid showed no increase in cells and the Wassermann reaction was negative but the protein was 80 mg. %. Two weeks later the protein was 60 mg. %, but the cerebrospinal fluid was otherwise normal.

BLOOD PICTURE

Red blood cells, 3,780,000 per c.mm.
Haemoglobin, 62% (Haldane).
Colour index, 0·82.
Reticulocytes, 5·5%.
White blood cells, 8,200 per c.mm. (Polymorphs 25%, eosinophils 1%, basophils 1%, lymphocytes 58%, monocytes 13%, myelocytes 1%, Türk cells 1%.)
A few of the red cells were normal; the rest were severely microcytic and hypochromic. There was no punctate basophilia.

Skiagrams (Fig. 1) showed dense marginal bands at the metaphyses of all the long bones and also at the anterior ends of the ribs.

The changes in the long bones in conjunction with the convulsions, the raised protein in the cerebrospinal fluid, and the hypochromic anaemia were strongly suggestive of lead poisoning but the history at first gave no hint of any possible source of lead. Neither parent had suffered from any symptoms suggestive of plumbism, the child had been wholly breast fed until the onset of symptoms, no nipple shields had been used nor had any medicaments been applied to the mother's nipples. The child's age ruled out the possibility of any prolonged period of sucking painted articles. Eventually the

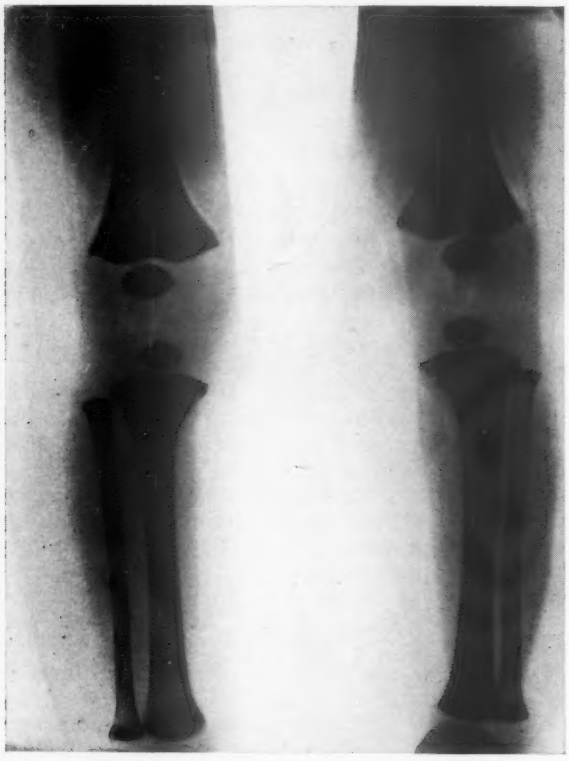

FIG. 1.—Dense bands at the metaphyseal borders on August 4, 1947.

mother volunteered that he had always been a very thirsty baby and since the age of 1 or 2 weeks had drunk about a teacupful of water daily in addition to his feeds.

Examination of specimens of tap water from the infant's home gave the following results:

Morning (first run off), 2·0 parts per 100,000.
After five minutes running, 1·4 parts per 100,000.
Maximum safe limit, 0·05 parts per 100,000 (Suckling, 1943).

On further inquiry it was found that about one year previously new lead pipes had been installed in the house (a gardener's cottage on an estate in Aberdeenshire).

By the time the diagnosis was established the acute symptoms had subsided and no treatment was considered necessary other than the administration of vitamin D in an attempt to hasten the deposition of lead in the bones. The infant was allowed to return home after the lead pipes had been replaced by asbestos piping and was seen again as an out-patient on December 11, 1947, when he was keen, healthy and making normal progress for his age. Skiagrams of the long bones (Fig. 2) showed double dense lines in the metaphyseal regions, one at the original site, now left behind in the shafts of the bones as a result of growth, and one at the metaphyseal borders. In view of this finding the possibility of further absorption of lead was considered but tests of the water supply showed it to be free from lead.

The baby remained under observation until June, 1949. During this period his general progress has been very satisfactory apart from some delay in his speech which is, perhaps, slightly behind the average for a child of his age. Skiagrams at intervals have shown the continued presence of double metaphyseal lines of slowly decreasing density: the second line has remained at the margin of the metaphysis and the distance between the lines is accordingly increasing with growth.

Discussion

Source of Lead. The many and varied sources of lead poisoning in nursing infants have been well reviewed in the recent paper by Gordon and Whitehead (1949). In their full list of references, however, there is no mention of a case attributable to lead in the family water supply. I also have been unable to find any reference to such a condition in a breast fed infant. While the determining factor in producing acute symptoms in the present case was probably the change from breast to bottle feeding two weeks before admission, with consequent increase in the lead intake, it is certain from the width and density of the metaphyseal lines and also from the fact that the first symptoms appeared at the time of weaning that absorption of lead had been going on for considerably longer than two weeks. Before this, of course, the infant had been drinking a considerable quantity of water, but it is

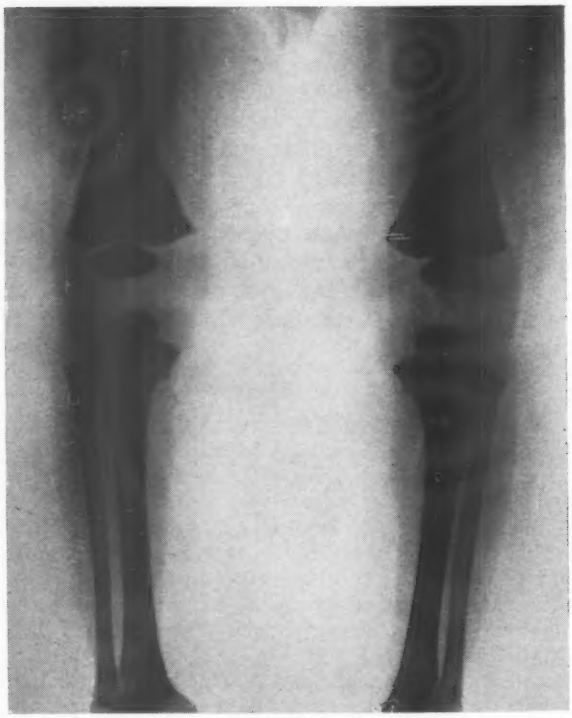

FIG. 2.—Double bands at the metaphyses on December 11, 1947. The original band is denser than the secondary band at the growing border.

possible that lead was also being secreted in the mother's milk. Dufour Labastide, quoted by Gordon and Whitehead (1949), recorded several cases of poisoning in infants due to secretion of lead in the milk of mothers poisoned by skin cosmetics and hair dyes. In view of the high concentration of lead in the water supply it is surprising that the only sign of poisoning in the parents was a slight degree of hypochromic anaemia in the mother. This supports the opinion of McKhann and Vogt (1933) that children are more susceptible to severe intoxication than adults.

Symptomatology. The earliest symptoms in this case were listlessness and vomiting. According to McKhann and Vogt (1933) gastro-intestinal upset is commonly the first sign of lead poisoning in infants, but it appears that this upset may be minimal and insufficient to make the parents seek medical advice, so that in many cases, as in this one, the infant will present with full-blown signs of encephalopathy, a much commoner syndrome in the child than in the adult. Peripheral neuritis, which is the commoner form of involvement of the nervous system in the adult is rarely met with in the child.

The blood picture in this case did not show the punctate basophilia commonly seen in the red blood cells in chronic lead poisoning. As McKhann and Vogt (1933) point out, this is not a constant feature of the disease and is in any case not confined to lead poisoning. The moderate degree of hypochromic anaemia combined with a reticulocytosis seen in this case illustrate the other features of the usual blood picture in plumbism.

Radiological Findings. In retrospect the diagnosis of the present case appears fairly obvious. At the time of admission, however, the problem was by no means so simple, and the diagnosis might well have been missed but for the radiologist's report of the presence of dense bands at the anterior ends of the ribs and at the inferior angles of the scapulae noted in a skiagram of the chest taken to exclude pulmonary disease as a factor responsible for the convulsions. This finding led to systematic examination of the long bones with the result that similar bands were found at all the metaphyses, most marked at the lower ends of the radius, ulna, and femur and the upper end of the tibia. Dense bands at the metaphyseal borders were first reported in lead poisoning by Vogt (1930) and Park, Jackson, and Kajdi (1931), and are discussed at some length by Cooper (1947); they are present where bone growth is most active and are thought to be due to crowding together of the trabeculae and concentration of lead, which is deposited most readily in growing bone. Cooper states that similar zones of increased density in the metaphyses may also be produced by poisoning with bismuth and inorganic phosphorus, by congenital syphilis, and by a few other rare conditions, and may occasionally be met with in normal metaphyses. While the diagnosis of lead poisoning cannot be made from the radiological findings alone, he considers that ' in children metaphyseal densities in the most actively growing bones are the most consistent and reliable evidence available.' He reports a series of 19 cases due to inhalation of fumes from burning discarded battery cases; of this series only the two oldest, aged 17 and 20 years, and the two youngest, both aged 3 months, showed no radiological changes. According to Kasahara quoted by Cooper (1947) skeletal changes appear at the age of 5 to 6 months in breast fed Japanese infants poisoned by the excretion of lead in the milk of mothers who use lead-containing cosmetics extensively. The well-marked metaphyseal lines in the present case would appear, therefore, to have developed at an unusually early age.

The double zone of density seen in the present case (Fig. 2) is also mentioned by Cooper (1947) who suggests that it may be produced by further episodes of lead absorption or by a temporary increase of the amount of lead in the blood as a result of mobilization of lead previously deposited in the bones. Aub, Fairhall, Minot, and Reznikoff, (1925) have pointed out that, in general, the absorption, transport, deposition, and elimination of lead follows closely that of calcium and that factors influencing the metabolism of calcium also influence that of lead. Administration of calcium and vitamin D promote the deposition of lead in the bones where it is inert and harmless, and consequently its removal from the blood and soft tissues. Conversely the administration of parathormone or a low calcium diet or the production of acidosis will result in the mobilization of lead from the bones into the blood stream whence some of it will be eliminated by the bowel and kidneys, and some will be deposited in the soft tissues. Lead so mobilized but not excreted will presumably in the course of time tend to be re-deposited in the growing bone ends.

It is interesting in the present case to follow the progress of the two lines at each metaphysis through a series of skiagrams taken at intervals of a few months. The original line, as might be expected, has been left behind in the shaft of the bone by the process of growth; the second line, first noted in December, 1947 (Fig. 2) remains at the metaphyseal border throughout a series of skiagrams taken in February, June (Fig. 3), and September, 1948. In December, 1947, the original line is the denser of the two but in the succeeding skiagrams the second

or marginal line is considerably denser than the original one, which has, in fact, almost disappeared by September, 1948. The fact that the second line has remained at the metaphyseal border over a period of nine months proves that it cannot in this

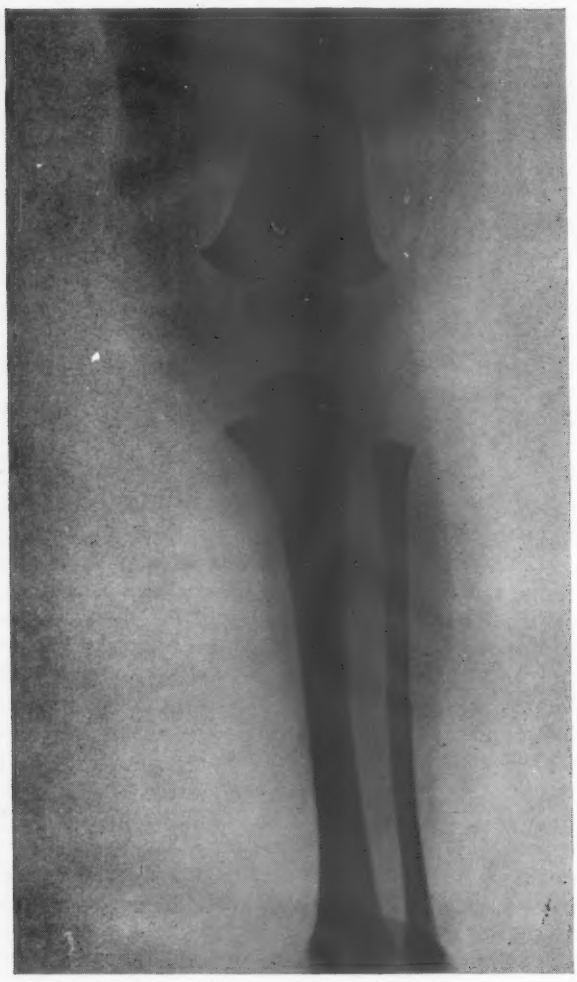

FIG. 3.—Double bands on June 7, 1948. The original band is now fading in the shaft of the bone and the secondary marginal band is the denser of the two.

case be the result of an isolated period of ingestion of lead or of mobilization of lead from the bones. The most likely explanation would seem to be that there is a continual slow mobilization of lead from the original depots after growth in that particular zone has ceased and a persistent tendency to deposition in growing bone.

Management and Prognosis. Theoretically it is desirable to eliminate the lead from the body as soon as possible for, while the lead in the bones is inert and harmless, it may at any time be mobilized as a result of acidosis with the result that, if the blood concentration rises sufficiently, fresh signs of poisoning will appear. In practice, however, it appears to be generally agreed that attempts to promote rapid elimination of lead by administration of parathormone or low calcium diet or acid-producing salts are fraught with considerable danger, particularly in children. It is difficult or impossible to control the rate at which lead is released into the bloodstream, and at any time the concentration of lead in the body fluids and nervous system may rise to a sufficiently high level to produce a fresh attack of encephalopathy with all its dangers, immediate and remote. It would seem safer to promote the deposition of lead in the bones by giving adequate amounts of vitamin D and allow elimination to proceed slowly and gradually over a period of months or years, as it will, provided there is no further ingestion of lead.

The immediate treatment of established encephalopathy is unsatisfactory. Repeated lumbar puncture, the administration of magnesium sulphate by enema or intramuscular injection, and hypertonic glucose or saline solutions intravenously, have all been recommended for the reduction of the cerebral oedema but are of doubtful value. The convulsions are difficult to control by the usual sedatives, which in any case do not affect the underlying pathological process. As the symptoms of encephalopathy in the present case had subsided before the diagnosis was established, the question of treatment of the acute state did not arise.

The prognosis of lead poisoning in infancy is poor, and, where encephalopathy is present, the immediate mortality is high. Holt (cited by Ford, 1945) reported 13 deaths within a short time of admission among 20 children with convulsions due to lead encephalopathy. Of the seven survivors two were idiots and three more mildly mentally defective, one showed difficulty in gait, and only one was restored to normal health.

Byers and Lord (1943) surveyed a series of 20 children of school age who had been admitted to the Children's Hospital, Boston, some eight years previously with lead poisoning. Of these children only eight had shown any evidence of encephalopathy and none of these were really severe examples of the condition. All 20 were considered to have recovered completely when they were discharged from hospital, yet only one was making satisfactory progress at school at the time of re-examination, and the majority of them showed evidence of intellectual or emotional difficulties. The authors considered that all these children were mentally normal before their episodes of lead poisoning but

from their paper it appears that in three cases aged 4 years or over at the time of the original admission the poisoning was the result of sucking lead paint. Whether a child of this age who sucks paint to the extent of developing lead poisoning can be considered mentally normal would appear to be a debatable point, but even if these three cases are discounted the after effects in the remainder are still discouraging.

The present patient is fortunate in having made a good recovery and shows no signs of permanent damage to the central nervous system, although the slight delay in speaking may be due to some mental retardation. His behaviour is otherwise perfectly normal, however, and it seems likely that any mental backwardness must be very slight.

Summary

The infrequency in the British literature of case records of lead poisoning in infancy is commented on.

A case of lead poisoning with encephalopathy in a young infant is described.

Although the lead was derived from the domestic water supply, the other members of the family showed no overt signs of poisoning.

The changes in the bones which, after radiological examination, first drew attention to the diagnosis are described.

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A REVIEW OF INFANTILE ACRODYNIA ('PINK DISEASE')

BY

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Selter (1903, 1927), who first described the syndrome of infantile acrodynia clearly, had by 1927 recognized that the apparently incoherent multitude of functional disturbances could be satisfactorily explained as due to autonomic dysfunction, and used the term vegetative neurosis. A groping towards causation has only been possible by a process of exclusion. The concept of diet deficiency, for example, has been abandoned, attractive as it seemed at one time, partly because the disease, whether in symptoms or pathology, resembles no known deficiency disease in man, and partly because it is found very frequently in conditions which seem to preclude malnutrition. The limits of age within which authentic cases have been reported are from the third week (Wyllie and Stern, 1931) to the fourth year; above this age there are probably a few cases which would be recognized by paediatricians or neurologists as falling within the descriptive category, but none of the cases described in later childhood reproduce the typical picture of infantile acrodynia, and the very rare cases reported in adults (White, 1926) rest on insecure evidence. This is not to say that it is impossible for the disease to occur at other ages with a rather different appearance; indeed it is unlikely that a disease which appears not to have its origins in prenatal life or birth itself should be confined to the first four years.

The symptoms of acrodynia as they appear to the physician may be grouped roughly as follows:

CARDIOVASCULAR. Tachycardia, hypertension; occasionally epistaxis, melaena, gangrene.

EMOTIONAL. Depression, apathy, fretfulness, perversion of appetite, loss of interest, insomnia.

NERVOUS SYSTEM. Myasthenia, hypotonia, photophobia; sweating, incontinence; head-banging, rocking and salaaming; paraesthesia, possibly 'thalamic' pain; disturbed temperature regulation; occasionally tremor, convulsions.

SKIN AND MUCOSAE. Erythema, swelling of hands and feet; ulceration of mouth, loosening of teeth; dystrophy of nails and hair.

METABOLIC. Hyperglycaemia, glycosuria; loss of weight; increased basal metabolic rate; enlargement of liver.

ENDOCRINE. Cessation of growth; diuresis.

DIGESTIVE. Vomiting, diarrhoea; occasional prolapse of rectum; occasional intestinal spasm, rarely progressing to intussusception.

BLOOD. Neutrophil leucocytosis.

I have records of 31 personal cases, the youngest being 4 months, the oldest 3 years at the onset. The age distribution is shown in Fig. 1. The sexes

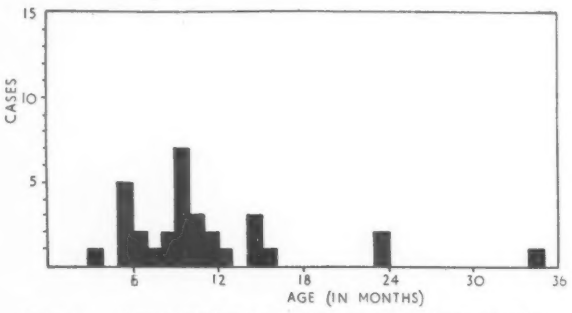

Fig. 1. Age distribution of 31 cases of acrodynia

are equally affected in this group, as in other analysed series (Logan, 1949).

There have been many good descriptions of the symptoms, so it is unnecessary to recapitulate them, but it is worth while to emphasize some of the features. The earliest are emotional: a lively baby becomes increasingly apathetic, loses interest in its surroundings, ceases to play, sleeps little, cries a lot. Older children cease to stand or walk or talk, and do not resume their progress in activity until the illness is past. No smile can be provoked, and the child resents being lifted or handled unless to be nursed very quietly. The earliest symptom of recovery is an improvement in mood and interest.

Sweating is not invariable, but is sometimes excessive and prolonged. The only one of my cases to have obviously severe colic was the oldest, a child of 3 years, but one suspects that colic is not

uncommon. The temperature is usually raised (invariably in my cases), but occasionally subnormal (Feer, 1935). The hypotonia is profound; a tentative diagnosis of myotonia congenita had been made in one of my cases, and no other disease produces such severe generalized loss of tone. But although immobility in the characteristic flexion position (occasionally opisthotonic) is preserved for hours without true sleep, the child will struggle on occasion and actual paralysis is never present. Tendon jerks were preserved in all but one of my cases. Tremor and convulsions have been described, and also facial palsy (Wyllie and Stern, 1931), but I have not seen either.

A heart rate of 120 to 140 (much higher rates occur) is such a constant feature that one would hesitate to diagnose in the absence of tachycardia. The raised blood pressure is another useful diagnostic point. Bowman (1933) found the normal neonatal pressure to be 64/44. Allen-Williams (1945) made it 90/60 in the second half of the first year, rising to 100/65 at the end of the year. I have reasonably accurate measurements in 18 cases as follows:

Maximum systolic pressure:

	150	140	130	120	110	100	90	80
Cases:	1	1	4	4	1	2	4	1

Judging by the way in which some of the children rub their hands and feet, paraesthesia must be severe, but the skin is not necessarily hypersensitive; indeed some children seem to like to be stroked or rubbed, and it is probably for the sake of coolness rather than to escape pressure from the bedclothes that they crawl out from under them. Both appearance and symptoms in hands and feet are at times reminiscent of erythromelalgia. Movement of the joints is sometimes resented. Gareau (1942) considers lymphadenopathy common.

The rash varies: it is more obvious in older children, and in young babies is more or less limited to the hands and feet, which are swollen but do not pit on pressure. The colour of the hands and feet may be normal, red, or cyanotic. A three-year-old child had swellings in various parts of the body (elbow, forehead, legs) and purpura. The usual rash is erythematous, persistent or recurrent, macular or confluent, and some desquamation is invariable. The rash may appear early, or not until other symptoms have been present for some weeks.

Two of my cases lost some of their teeth, and one of these had atrophy of the nails and lost his scalp hair. Gangrene has been described (Weber, 1922; Feer, 1935; Rocaz, 1936). This group of symptoms is probably to be ascribed to ischaemia from vasospasm. Stomatitis and gingivitis are secondary phenomena.

Functional Pathology

No other disease is described, at any age, in which such perverted function of the vegetative nervous system is seen as a clear picture, with the possible exception of hyperthyroidism. In the latter condition, however, it is the orthosympathetic alone which is disturbed, whereas in acrodynia the symptoms can only be explained by a disturbance of the whole autonomic system. It is impossible, and unnecessary, to suppose that this disturbance is peripheral; there is only one site in the body which can be regarded as regulating the autonomic in such a way as to cause such disorganization when it is itself the site of a pathological process, and this is the diencephalon. It would not in fact be inappropriate to speak of acrodynia as 'diencephalopathy.'

All the primary features of acrodynia have been described as following local disease processes or experimental interference with the hypothalamus. The form of this region of the brain undergoes important changes during growth, assuming a position in the economy of the nervous system which is decreasingly important as adult life is reached. It would perhaps be better to say that in adult life the part the hypothalamus plays in the behaviour of the whole organism is less in evidence, overlaid by systems of later functional development. Anatomically, it is a more complex structure in the embryo than in the adult and represents an extension of olfactory function, concerned with emotional life. Grinker (1944), who regards the hypothalamus not as having a multitude of functions spatially separated in terms of cell groups (an almost impossible conception in relation to its size), but as a balancing mechanism, believes that there are nevertheless two general systems contained within it, acting reciprocally, the posterior orthosympathetic and the anterior parasympathetic. He classifies the influence of this regulating mechanism under four heads: (1) endocrine, (2) emotional, (3) awareness or attention, and (4) autonomic, mediated through the pituitary, the vagus, the thalamus, the thoracic sympathetic outflow. The information comes partly from destructive lesions occurring naturally (tumour, encephalitis) and partly from experimental physiology. A monograph by Le Gros Clark, Beattie, Dott, and Riddoch (1938) surveyed this field. The relevant results of proved hypothalamic disturbances are as follows:

ENDOCRINE. (*a*) Emaciation; (*b*) diuresis; (*c*) diabetogenic; (*d*) adrenal cortical depression; (*e*) arrest of growth.

EMOTIONAL. Depression, irritability, lack of emotional expression, possibly 'rage attacks.'

ATTENTION. (*a*) Hypersomnia, catalepsy, disturbed

sleep rhythm; (*b*) apathy, loss of interest, passivity.

AUTONOMIC. (*a*) Hypertension due to arteriolar contraction; (*b*) tachycardia; (*c*) contraction of bladder and intestinal muscle; (*d*) excessive tears and saliva, sweating; (*e*) disturbed temperature regulation.

Thus all the symptoms of infantile acrodynia are comprehended in the effects known to follow abnormal function of the hypothalamus, with the exception of anorexia, hypotonus, photophobia, and the skin lesions. Attacks of tonelessness (kataplexy) are closely associated with hypersomnia; hypothalamic pathology in this condition is unproven, but generally assumed. A 'functional' hypothalamic disturbance as the mechanism of anorexia nervosa has been postulated. The 'erythro-oedema' of acrodynia suggests arteriolar spasm; the photophobia, which is not accompanied by any evidence of an inflammatory condition, is perhaps explained as the result of slow contraction of the pupil to light. Day, Smith, and Klingman (1939) have carried out some experiments which tend to show that the autonomic nervous system is unresponsive to normal stimuli in these children. Cheek and Hicks (1950) have shown in a series of cases that the blood sodium chloride is depleted; their patients improved rapidly when given salt and desoxycorticosterone. They suggest that the salt depletion is due to adrenal failure and that the 'erythro-oedema' is a sign of disturbed water balance.

Epidemiology

There have been many contributors to the literature of this subject whose interest has been roused by groups of cases seen in a relatively short space of time. Bilderback (1946) represents opinion in the United States when he says categorically that this is a sporadic, not an epidemic disease. But he notes that it appears to have a local incidence, being more common in Europe, and especially in Great Britain, than in the U.S.A., tends to occur in the country and in small towns, and agrees that cases are often seen in groups.

> 'It has been the experience of many clinicians that they may see a number of cases of acrodynia within a few months and not observe one again for several years.'

Spitz and Wolf (1946) describe under the title 'anaclitic depression' what was almost certainly an outbreak of the disease in a nursery affecting 19 out of 123 children.

Case reports were common and interest widespread in the period 1914-30. Swift (1918) reported a group of 14 cases in Australia in 1914, and this was rapidly followed by descriptions of similar groups, usually of 10 to 12 cases, in various parts of the world. This 'outbreak' seems to have died down about 1925, but in the decade 1935-45 increasingly frequent reports suggested a recrudescence in America. Zahorsky (1937) described 60 cases which he thought were grouped in 'island' fashion (a phenomenon previously described by Péhu and Boucomont 1936), and was considered due not only to geographical but to racial causes, since in his group he found no Jewish patients, although more than a third of his practice was among Jews. This might equally well have been due, however, to differences in custom or diet. A large number of cases were seen and described during the years immediately following the 1914-18 war, and coincided with the influenza epidemic. The relationship of acrodynia as described in the twentieth century, beginning with Selter's account of eight cases in Germany in 1903, to a disease occurring in much more widespread form during the nineteenth century in France (in particular a description of an epidemic in 1830) is too vague to be worth serious consideration, although some authors have considered them related or identical (Craig, 1927). I have not been able to obtain a copy of Chardon's description of this outbreak which is referred to by several writers (Chardon fils, 1830), but it seems unlikely that the data could be enough to establish it as the same disease. It was apparently estimated that about 50,000 cases occurred in France at this time, and no 'outbreak' of acrodynia with numbers approaching this figure has ever been reported in any other part of the world.

Regional Distribution of Mortality Statistics

Logan (1949) analyses the death certification of acrodynia in England and Wales from 1923 (when the first case was recognized) to 1947. By 1926, when there was general appreciation of the diagnosis, there were 20 certified deaths, and thereafter a slow rise in numbers to a peak of 88 in 1936. The figures for 1937-39 were 73, 81, 69, but fell to a steady level near 50 for 1940-46, with an abrupt rise to 103 in 1947. Regional analysis for the years 1940-46 shows a general tendency (which is statistically significant) for more cases to occur in the north than the south, with the lowest incidence in south-west England.

Seasonal Incidence

The disease is generally thought to appear more commonly in the spring and summer. The main incidence has been considered by Blackfan and McKhann (1933) to be February to June, by

Braithwaite (1933) March to October, by Groom (1941) January to June, and by Selter (1927) January to May.

The seasonal onset of my 31 cases is shown in the table. In this group, spring and early summer show most cases, but it is perhaps significant that the cases seen in south England show this clearly, whereas the Scottish cases are more nearly distributed throughout the year.

In the period 1939-45, I observed 16 cases in the Highlands of Scotland. My position was exceptional in that I was the only consulting physician working in this relatively isolated area, and although I am not confident that all cases in the Highlands, even perhaps grave ones, came to my notice, I believe it to be unlikely that many were missed. The distribution of these cases corresponded roughly to the population density of the whole region; they were not concentrated in the towns. The time sequence, however, may be of significance; this is a condition which has interested me for more than 20 years, but in the period 1931-38, working in a Midlands industrial area with a large children's clinic and with the charge of 20 paediatric beds, I saw only three or four cases. In 30 months' paediatric practice in Kent, with patients drawn mainly from the densely populated outer suburbs of London, I have seen 15 cases. The distribution in years is shown in Fig. 2.

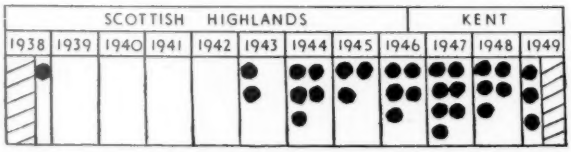

Fig. 2. Distribution in years of 31 personal cases of acrodynia.

From the published data, one must conclude that nothing approaching an epidemic has been reported, but the case incidence is certainly compatible with an infective or toxic cause with periodic enhancement of risk and widespread immunity.

Infection

Contact cases are unknown. Attempts to obtain evidence of the infective nature of the illness have been made through examination of the spinal fluid, which is rarely found to be pathological by the methods of analysis in current use. Occasionally a slight increase in protein or cells has been recorded early in the disease (Rocaz, 1933; Blackfan and McKhann, 1933). Five of my cases showed completely normal cerebrospinal fluids at the time of diagnosis. Many observers have believed a virus infection to be likely (Cobb, 1933), and others have thought that preceding bacterial infection was frequent (Rodda, 1925). It was mentioned in only four of my cases.

More than One Case in a Family. This has been reported so often as to be recognized as a common feature of any considerable series of cases (Wood and Wood, 1935; Clements, 1940; Gareau, 1942; Kniper, 1927). Two of my cases belonged to one family; the second child developed the disease more than four years after the first and was not born until after the first had fully recovered.

Morbid Anatomy

This is particularly difficult ground. The protracted illness, with emaciation, gives obvious opportunity for secondary infection, and in most of the reported necropsied cases bronchopneumonia was present. This has been thought by many to invalidate the supposed specificity of the morbid histology reported, especially in the spinal cord. The term 'erythro-oedema-polyneuritica' has been used fairly widely to describe the condition, a name based partly on the evidence of peripheral neuritis found at necropsy. Paterson and Greenfield (1923) described demyelinization, especially of the smaller fibrils in limb nerves, lymphocytic infiltration, and chromatolysis of anterior horn cells. One of their cases which showed the most striking changes of this type had died of miliary tuberculosis. It is not possible at present to state what constitutes a nonspecific, toxic or allergic change in the histology of the nervous system, and others have not been able to confirm the findings of demyelinization in the peripheral nerves. No changes considered at all specific were found by Wyllie and Stern (1931) in seven necropsies, or by Blackfan and McKhann in five. Orton and Bender (1931) reported degeneration of lateral horn cells which they considered to be the effector cells of the splanchnic sympathetic; they were impressed by the clinical and pathological resemblances between cases of acrodynia and pellagra.

Francioni and Vigi (1928) described the syndrome of acrodynia appearing in a child convalescent from what they believed to have been epidemic encephalitis; this child, four years old, died of the disease and they discovered degenerative changes in the infundibulum and tuber cinereum. Cobb (1933) in a critical review of these findings, was inclined to accept those described by Orton and Bender and by Francioni and Vigi, but to reject those of Paterson and Wyllie as nonspecific. Warthin (1926) found no evidence of polyneuritis, but spinal cord changes which he also thought to resemble closely those of pellagra. Both of his subjects died of pneumonia. Bilderback (1946) considers that

published reports give no good evidence of specific changes at all and remarks that an ' organic ' disease with such constant clinical phenomena would certainly be expected to produce definite histological changes. A necropsy on one of his cases is reported in detail, with the conclusion that nothing was seen which might not also have been observed as a result of any long exhausting illness.

It is clear that the number and range of observations are far too limited for any conclusions to be drawn; it is doubtful whether purely histological study, at least by existing techniques, will correct this deficiency, but clearly important that attempts should be made. The clinical evidence suggesting somatic neuropathy is slight and in view of the facts pointing to disturbed hypothalamic function, it would seem that attention should be concentrated on the diencephalon.

Nutrition

The evidence for regarding acrodynia as wholly or partly due to nutritional defect rested first on the resemblance of acrodynia to some types of vitamin B deficiency, and secondly on the supposed similarity of the spinal cord histology in acrodynia and pellagra. Anorexia, polyneuritis, apathy, and depression are features of both thiamine and nicotinic acid deficiency; hypotonia and photophobia have been described in ariboflavinosis. There are at least superficial resemblances between the chronic dermatitis of pellagra and the exfoliative stage of acrodynia. Orton and Bender (1931), who described destructive lesions in the lateral horn cells in a fatal case of acrodynia, considered them almost identical with those found in adult cases of pellagra in which severe anorexia, psychosis, dermatitis, diarrhoea, peripheral neuropathy and trophic lesions had been present. Warthin (1926) was of the same opinion. But many of the symptoms of vitamin B deficiency are lacking; there are no lesions of the tongue or cheilosis, the photophobia is not associated with other changes in the eye, and clinical signs of peripheral neuritis are slight or absent.

The nutritional history of most cases is above suspicion; the disease has often developed in children who were entirely breast-fed by mothers in good health. Further, therapeutic tests should by now have put the matter beyond doubt, and these have been on the whole negative. Many physicians claim improvement by using thiamine, but their tests have not been well controlled. Tisdall, Drake, and Brown (1938) used nicotinic acid without evidence of improvement. Forsyth (1941) thought he obtained some benefit from wheat germ, but none from yeast extracts, and suggests vitamin E deficiency as the cause. The rather abrupt onset of symptoms is against a dietetic cause, and there are many features of the disease which bear no relation to any known diet deficiency syndrome (for example the persistent rise in blood pressure). I have used thiamine, pyridoxine, calcium pantothenate, and riboflavine, without appreciable results.

Poisons

Some resemblance has been noted between the symptoms of acrodynia and those of rye fungus poisoning (ustilaginism), but the existence of typical cases in wholly breast-fed children makes any theory based upon this untenable. Clements (1940) thought it worth while, however, to carry out some experimental work on mice with rye fungus, with negative results. The disease seen in rats due to ' egg white injury,' resulting in biotin deficiency, has also been thought to bear a resemblance to infantile acrodynia (Findlay and Stern, 1929). Recently, it has been suggested that poisoning or idiosyncrasy to mercury may be the fundamental cause. (Warkany and Hubbard, 1948; Bivings and Lewis, 1948; Bivings, 1949.) The idea is not new, since it was apparently considered a possibility by Zahorsky in 1922. The resemblance to classical mercurial poisoning is slight; many infants are still given mercury by doctors, nurses and mothers, either as ' grey powder ' or ' teething powder,' yet acrodynia is an uncommon disease. In cross-examination, mothers of some recent personal cases have denied any such treatment, and there seems no reason to doubt their word. The evidence, in fact, rests upon the microanalysis of the urinary output of mercury. Bivings and Lewis (1948) found 100 γ of mercury per litre in the urine of a girl of 6 months with acrodynia, and none two weeks later, after she had been treated with BAL (British anti-Lewisite). The disappearance of the mercury coincided with clinical improvement, but the duration of her illness is not stated; residual photophobia was thought to be due to iritis and was cured by atropin. Bivings subsequently collected data on 44 cases, in 28 of which mercury had either been administered or found in the urine; in three of the remainder, the urine was free from mercury (Bivings, 1949). The source of the mercury was thought to be teething powder, but mercury ointment and corrosive sublimate had been used locally in other cases. Warkany and Hubbard (1948) considered amounts of over 50 γ per litre of urine, as determined by their technique of analysis, significant of intoxication. Control cases rarely showed this amount. The maximum found in a case of acrodynia was 360 γ per litre; no other case showed more than 100. Excretion seemed to be erratic, and was present in some cases for months.

Teething powders had been used in three recent

cases seen by me; in the urine of one of these, and also in the urine of another case without reliable history, mercury was found in amounts not exceeding 100 γ per litre; in two further cases, teething powders had been used, but not until after the development of symptoms. Much work will be necessary before the significance of these results can be estimated. They have called attention to the extraordinary prevalence of the use of mercury in infancy and surveys will be required both of the use of teething powders and of the normal incidence of mercury in the urine. With the help of members of the county child health staff in Kent, an enquiry was made of 100 mothers of children aged between 12 and 24 months. Forty-eight of them had used powders containing calomel, and another four had used grey powder. The powders had often been given every week from a very early age. None of these children showed symptoms of acrodynia (Leys, 1949).

The excretion of other trace metals in the urine of children with acrodynia must be determined also, since diuresis is probably a constant feature of acrodynia and there is also serious metabolic derangement. Annual, regional, and seasonal incidences are difficult to reconcile with such a cause. Arsenic has also been incriminated (Calvin and Taylor, 1935).

Allergy

This overworked word badly needs redefining, but the present state of our knowledge hardly allows of this, and in the meantime we must continue to use it in a descriptive sense. The idea that acrodynia may be regarded as an allergic phenomenon has been held with great tenacity by some observers (Helmick, 1927) and certainly there are many symptoms which suggest the connexion; the rash, which will often continue for weeks, although never frankly urticarial, is not unlike that seen in some types of chronic allergy. Eosinophilia is not seen, nor has anyone produced evidence of the 'allergic constitution.'

Emotional Factors

I believe the initial symptom in every case to be loss of affect; this, and refusal of food, are the things which most distress parents. The general appearance of the fully declared case is either one of deep depression or of apathy; although the children are often said to be irritable, they are not restless, but passive; fretful crying seems rather a sign of discomfort unrelated to the environment. Many show no sign, beyond a languid movement of the eyes, that they are aware of your approach, and the best efforts to amuse do not bring a smile, or any indication of interest when toys are offered. The degree of this 'withdrawal' varies in duration and intensity; in the worst cases it continues for months or until death. The advances of the infant's mother often seem no more welcome than those of a stranger. I have seen infants almost *in extremis* from infection or severe anaemia, who still maintained an active interest in their surroundings. To watch the child with acrodynia is to receive a very deep impression of a primary emotional disorder. Revival of interest is an absolute indication of ultimate recovery, although full health may still not be regained for many months.

Under the title of 'anaclitic depression' Spitz and Wolf (1946) describe a syndrome which occurred among a group of infants in a nursery and foundling hospital; the nursery children were temporarily and the foundlings permanently separated from their mothers. There were 19 cases among 123 infants who were under observation, and at the onset of the syndrome the youngest child was 5 and the oldest 11 months old. The duration of the illness in recovered cases was something over three months, and the authors believed that restoration of the infant to its mother was the signal for improvement. The most serious cases were in children separated from mothers who had been particularly devoted to them. No analysis of mortality is given, but several of the foundling children died; arrested development in behaviour was noted among all those affected. Spitz and Wolf considered this illness to be comparable to melancholia in the adult and caused by 'withdrawal of the love object.' They compare the refusal of food and susceptibility to infection, which were characteristic of their cases, to suicidal tendencies in the adult, a 'hostile' deprivation taking the place of the destructive power of the superego. In other words, they considered the infants to be suffering from a psychosis, the result of a violent change in environment.

The authors of this paper are psychoanalysts, and seemed to be unaware that these children might be suffering from the condition called for so many years by paediatricians acrodynia, yet their description leaves no doubt of it. The infants 'lost their happy and outgoing behaviour,' refused food, lost weight, showed 'increased susceptibility to colds and eczema' and developed a 'sort of frozen rigidity of expression.' They noted a reluctance to touch objects, a preference for lying on the face, bizarre hand and finger movements, a 'stuporous catatonia.' They describe the syndrome and its apparent cure by restoration to the mother or successful substitute for mother-love, in purely psychiatric terms and although in their limited follow-up recovery was apparently complete, they suggest that a distortion of personality of this order

is likely to leave its permanent mark on development. While the oblivion of these authors to previous clinical description is as regrettable as the ignoring by clinicians of psychiatric implications, their analysis demands a serious consideration of acrodynia as a psychosomatic disease, in spite of some obvious objections, such as differences in regional incidence.

Psychiatrists, as a result of their case analyses and on theoretical grounds, deplore unnecessary admission of young children to institutions. Some physicians have long preached the same gospel as a result of clinical observation; such teaching in fact is acceptable to most children's doctors and experienced children's nurses, who have seen children die in hospital believing (and not on the grounds of risk of infection) that they would have lived had not mother-love, or the best substitute for it, been lacking. We know that the end result of emotional disorder can be death or grave disability from physical disease, as in duodenal haemorrhage, ulcerative colitis, coronary sclerosis. The mechanism may be slow in development. There is, in fact, nothing outrageous in the conception of acrodynia as a primary emotional disorder, and Feer's use of the term ' vegetative neurosis ' implies that he had this conception in mind. That psychic trauma in infancy should show itself, lacking the possibility of expression in words or more complex behaviour disorder, as a major disturbance of hypothalamic function, is rather to be expected. Acrodynia, however, is not confined to infants who have been separated from their mothers; on the contrary, 20 of my 31 cases developed in children who were in their mother's care. It so happened that the research undertaken by Spitz and Wolf was concerned with deprived children. If the interpretation of these authors that ' anaclitic depression ' is directly caused by physical separation of mother and child is wrong, are there circumstances in sporadic cases from which an equivalent profound emotional disorder could follow ? It is beyond my powers to discuss this question, nor was the possibility in mind when most of my cases were seen. Weaning is noted as immediately preceding the onset in only four cases, and others had developed the syndrome while still at the breast, or had been bottle-fed throughout. The peak age incidence, however, closely follows the weaning age. But if ' mourning ' can occur in the infant, its cause may no doubt be much more subtle than the physical removal of the mother or her breast, and to explore such a field may perhaps be as profitable as the estimation of mercury in the urine. In four cases the mother was physically or emotionally ill; the father was absent or dead in five others. I have reliable notes of the order of the family in 24 children, of whom 14 were first-born, eight second, and two third in the family. This distribution does not differ significantly from that of the general population in the last ten years.

Acrodynia-like Syndromes in the Adult

It would be surprising if any disease process not directly following from prenatal causes or birth trauma, were confined to early childhood. Symptoms, however, are likely to differ, and if no authentic cases of the fully developed syndrome of acrodynia have been recorded in adults, it may yet be worth while to consider whether there are syndromes which recall it. The signs and symptoms in the extremities are reminiscent of erythromelalgia. More suggestive, however, is the condition called neuro-dermato-myositis. This occurs in two forms, acute and chronic; the first is sometimes apparently epidemic (Williams, 1941) but sporadic cases with photophobia occur (Leys, 1942). The chronic form is a grave condition of gradual development leading on to sclerodermia and sometimes to gangrene, and its symptomatology includes acrocyanosis ; acroparaesthesia; tenderness of skin and muscle; sweating; rashes of various types, including urticaria, purpura, erythema, pemphigus and erysipeloid eruptions ; salivation ; dysphagia ; peripheral oedema ; areflexia ; hypotonia and myasthenic paresis ; hypertension ; raised metabolic rate ; the Raynaud phenomenon sometimes proceeding to gangrene ; arthropathy ; pigmentation and thickening of the dermis, sometimes proceeding to calcinosis (Sheldon, Young, and Dyke, 1939; Hendry and Anderson, 1939; Dowling and Griffiths, 1939; Dowling, 1939; Thomas, 1942). The aetiology is entirely obscure; the onset may be abrupt or insidious; the illness is of long duration and there is a considerable mortality. Partial syndromes of this type are not very uncommon, and may also appear as a sequel to encephalitis.

Complications, Prognosis and Treatment of Infantile Acrodynia

The mortality is low; there were no fatal cases in my series of 31 (nor among five further cases seen since this report was compiled), although death rates of up to 30% have been reported.

These children become emaciated; growth is retarded and there is complete arrest of progress in activity and often considerable regression, e.g. in equilibration. It is generally held that patients are especially prone to develop infections, but this was not a feature in my series; one of my cases had

definite bronchopneumonia. Many of the patients were treated in hospital, not always in isolation, and not under exceptionally favourable circumstances, in a mixed ward. The physical dangers of treatment in hospital are probably no greater than for other conditions; devoted nursing care is obviously important, and if weight loss can be prevented, the rapidity of recovery is obviously hastened.

Effect of Drugs. Many attempts have been made to influence the course of the disease, or of individual symptoms, by one or other of the many drugs acting upon the autonomic nervous system. Feer (1935) believed that atropine was of general value. Herz (1940) and Day, Smith, and Klingman (1939) both found that tachycardia was increased by it. Herz also had negative results from eserine and from acetyl choline given by iontophoresis. Ergotamine was used without good effect by Nelson (1937) and Feer (1935). Since many of the most unpleasant symptoms appear to be the result of arteriolar constriction, the choline group of drugs, which cause dilatation, would seem to be theoretically the most useful, but have the disadvantage of increasing smooth muscle tone in hollow organs. I have used carbaminocholine in several cases, in doses of 1 to 5 mg. orally, or 0·25 mg. by injection. The results were difficult to estimate; in two cases, lower pulse rates were seen; in one, this treatment coincided with rather rapid improvement, which was maintained, but was probably the result of the subsidence of the active cause. Looseness of the bowel prevented its continuance in other cases. Prostigmin has seemed to improve muscle tone in a few patients. More recently, I have used small doses of amphetamine because of its good effects in the depression of adults, but have not enough data to report upon its results. The giving of extra salt, as advised by Cheek and Hicks (1950), seems sensible, since salt is lost both by diuresis and by sweating and the intake is reduced; their use of desoxycorticosterone is more debatable. I have had the opportunity of treating one case only in this way; there was a small but definite gain in weight following salt therapy but this was not accelerated by injections of desoxycorticosterone (1·0 mg. on alternate days). The child became more energetic but in the course of a month there was no significant change in the general picture; the dose of sterone, however, was much less than these authors employed.

Some cases have a haemorrhagic tendency, not apparently connected with known vitamin deficiency; epistaxis and purpura of the skin occurred in one of my cases, and melaena in another, severe enough to require transfusion. Relapse is exceptional, but occurred once in this series of 31 cases. Ratcliffe (1941) found no evidence of lasting emotional disturbance in his cases, and this is the general experience; my own follow-up of cases only extends to 18 months, except in one case (five years); none has had any residual symptoms detected.

TABLE

SEASONAL ONSET OF INFANTILE ACRODYNIA

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Month
1938 ..												1	
1943 ..		1		1									
1944 ..						2	1			1		1	
1945 ..	1	1										1	
1946 ..			3		1		1						
1947 ..				2	2	2	1	1					
1948 ..			1		2		1						
1949 ..					2	1							
Total ..	1	2	4	3	7	5	4	1	0	1	0	3	
Scottish Highlands ..	1	2	3	1	1	2	2	0	0	1	0	3	
Kent ..	0	0	1	2	6	3	2	1	0	0	0	0	

Summary

A study of published cases of acrodynia and personal experience of a further 31, leads to the conclusion that this disease of infancy and early childhood should be regarded as a form of encephalopathy; the complex clinical picture can be satisfactorily explained by disturbed function of the hypothalamus, and the term diencephalopathy is suggested as a convenient descriptive term. The aetiology is still unknown and the possibility is discussed that this may be a primary emotional disorder. Attention is called to symptomatic resemblances between acrodynia in the infant and neuro-dermato-myositis in the adult.

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REVIEWS

Electroencephalography: A Symposium on Its Various Aspects. Edited by DENIS HILL, M.B., F.R.C.P., and GEOFFREY PARR, M.I.E.E. (1950). London: Macdonald and Co. (Publishers), Ltd. Illustrated. Pp. 438. Price £3 18*s*.

Most of the readers of this journal are concerned for the clinical aspects of children's diseases and they use biochemical and biophysical techniques in direct application to clinical problems.

This textbook, which is the first comprehensive and authoritative text on electroencephalography, may well daunt them, for the major and best part of it comprises a detailed account of the purely scientific background of the subject. The chapters dealing with the physiology by Dr. Whitteridge, biochemistry by Dr. Heppenstall, and pharmacology by Dr. Grevile comprise critical reviews of the first order and the introductory chapters dealing with the equipment, technique and interpretation give a most detailed and clear account of the physical basis of electroencephalography. Here the electrical analysis and synthesis of records shows to its best advantage, for the student can see how these complex and seemingly irrational tracings are made up of integrated sinusoidal waves, some of which can be correlated to clinical phenomena. The pattern of these waves is very different in childhood, and a fully mature series of records is not usually obtained until after puberty. The immaturity of children's records not only influences interpretation, but it also modifies the electrical response of the cortex to abnormal states such as epilepsy. This aspect of the subject is repeatedly illustrated in the text.

Where technical facts are concerned the book is admirable but it is weaker in the chapters dealing with clinical electroencephalography, perhaps because electroencephalographers are not clinicians, because clinicians have not sufficient electronic knowledge, or because the integration of clinical and laboratory data is still immature. Although Dr. Walter deals with the electroencephalographic phenomena found in epilepsy very carefully, all his illustrative records bear the tracings of electrical analysis of the electro-encephalogram which are not seen in many laboratories, so that their meaning is not at once evident. Similarly Dr. Cobb's chapters on tumours and trauma are mainly illustrated by records made with a two channel apparatus, which is unlike any equipment in use today. Because of these deviations from usual practice, and because of the weakness of the clinical correlates, these sections do not maintain the excellent standard of the entirely technical sections of the book. Dr. Hill does not have the same difficulty in dealing with his subject of psychiatry. He begins his admirable review by saying that ' at the outset it must be recognized that strictly within this field, disappointingly little has emerged ', and then goes on to integrate those advances which have taken place. This integrity of attitude in the difficult marriage between electronics and clinical medicine is one which too few have managed to attain.

The book is very well produced, fully illustrated, and includes technical appendices, an accurate index and a comprehensive bibliography, which is, however, being rapidly superseded. The need for the book will secure a wide sale.

Epidemics in Schools: An Analysis of the Data Collected during the Years 1935 to 1939. By E. A. CHEESEMAN. 1950. Medical Research Council Special Report Series No. 271. London: His Majesty's Stationery Office. Pp. 96. Price 3*s*.

Reports like this tend to correct ' impressions ' and to open new avenues to explore. In the former report covering 1930 to 1935, the assumption was made that measles would not spread if only a small proportion of susceptibles were present. Further figures in this report, which deals with the same schools from 1935-39, show that measles seem to spread even if there are a few in the school unprotected by a previous attack. Similarly it is stated ' from the very limited data available it would appear contrary to some opinion, that an attack of chicken-pox does not necessarily confer immunity from herpes zoster '.

The report has its limitations.

The foregoing paragraph:

' During the period 1935 to 1939 there were very few instances of measles exhibiting any of the more usual complications. Out of 786 cases recorded in boys' schools 14 (1·78%) also had associated otitis media and 12 (1·53%) developed pneumonia. In the period 1930 to 1934 the complications were slightly more frequent, the percentages being 2·7 and 1·9. In the girls' and naval schools the proportion of complications was negligible; 0·65% of measles attacks in the former were associated with otitis media compared with 3·1% in the earlier period while no cases developed pneumonia compared with 1% during the years 1930 to 1934,' stimulates the question: Is this because of the sulphonamides or in spite of them? Certainly in many areas sulphanilamide was not available in 1939.

One startling feature of the report is the relative figures for diphtheria, tuberculosis, and anterior poliomyelitis. In the naval schools averaging 1,300 boys, the boys' school averaging 4,000 and girls averaging 1,500, there were two cases of diphtheria in the naval, ten in the boys (four single and an epidemic of six) and nine in the girls. The incidence of anterior poliomyelitis was five (four in one boys', and a single case in another, boys' school). Tuberculosis caused two deaths from meningitis and four other cases in the naval school; 13 cases in the boys' and three in the girls' schools. Possibly three cases were doubtful, but to balance this

there were two pleural effusions and six pleurisys and six other cases which might well have been tuberculosis but not included. Even in the presumably well nurtured, 'the captain of the men of death' is at work, although trauma and lobar pneumonia claim more victims.

The report prompts us to ask, Why do some escape infection? Why is the proportion attacked fairly constant at a high level in measles, for example, whereas it is low or medium in others? And can we do anything active to prevent dysentery rearing its occasional ugly head, and to nip tuberculosis in the bud?

Human Milk. By S. K. KON, D.Sc., F.R.I.C., and E. H. MAWSON, M.A., Ph.D. 1950. London: His Majesty's Stationery Office. Pp. 188. Price 4*s*. 6*d*.

This work is the most comprehensive existing attempt to assemble average values for the constituents of human milk at various stages of lactation. Details of diets and income of the mothers, method of collection, and of analysis and so on are given and are of more than specialist interest.

There was an unexplained consistent difference in fat content of milks from Reading and Shoreditch mothers. The lactose content varies little. From experiments on rats it was concluded that the biological value of human milk proteins was not superior to those of cow's milk. The conclusion might have been more certain if the sugar contents of the diets had been made equal, for the rats on human milk all developed diarrhoea attributed to the high sugar content. A higher vitamin A intake in pregnancy has little effect on the amount secreted during lactation. The vitamin D content was very low, especially in winter. The vitamin B_1 level in the milk varied continually during the investigation. If results from other countries are comparable the B_1 content of milk is higher in this country than in Australia or in the U.S.A. which suggests that our war-time diet was good, though the average intake of B_1 by lactating mothers was considerably less than the amount recommended by the American National Research Council in 1943 and 1945. The B_1 content of the milk changed with changes in B_1 content of the diet though in a way difficult to define exactly, but there was a 'conspicuous and sustained rise in the vitamin B_1 content of the milk following the introduction of National wheatmeal bread'. The riboflavin values fluctuated widely with the amount of riboflavin in the mother's individual meals. On the other hand variations in vitamin C content are small, and the result on a single sample is significant. It appears that many nursing mothers take very little vitamin C. There was a rise in vitamin C content after the distribution of a consignment of oranges, 'showing that vitamin C supplements if taken by the mother rather than, as now, by the infant, would benefit both parties'.

The work has been admirably done and is well reported. Analyses of colostrum are not included. While the difficulties in collecting it are considerably greater, some members of the team, will, one hopes, attempt them.

Textbook of Pediatrics. By W. E. NELSON, M.D. 1950. Philadelphia and London: W. B. Saunders Co. 5th Edit. Illustrated. Pp. 1658. Price 63*s*.

'Mitchell-Nelson' needs no introduction to paediatricians. The fifth edition contains much new matter, and one must not complain at an increase in size of nearly 300 pages, for the standard is as high as before.

The Asthmatic Child: The Prevention of Asthma by Simple Home Methods. By G. F. WALKER, M.D., F.R.F.P.S.G., D.C.H., M.R.C.P. 1950. Bristol: John Wright and Sons, Ltd. Pp. 20. Price 2*s*. 6*d*. (25*s*. per doz.)

The exercises in this booklet are useful, but many paediatricians will disagree with some of the sweeping statements in the preface.

Child Development. By MARIAN E. BRECKENRIDGE, M.S., and E. LEE VINCENT, Ph.D. 1949. London and Philadelphia: W. B. Saunders Co. 2nd Edit. Pp. 622. Price 20*s*.

This is a good book well worth reading. 'The main reason for studying child development is to improve the lives of children . . . (this book) is designed for professional students in psychology, teacher training, home economics, medicine, nursing and social work as well as for parents.' It deals mainly with the school age and also briefly with earlier growth stages. Physical and emotional influences on growth are reviewed and the influence of nutrition and routines and of various groups with which the child is in contact. The development of memory, creative activity, personality, aggression, friendships, moral judgment, and psychosexual development are illustrated from widely selected references.

It is a long book but the more readable for this. The examples given on pp. 111 and 195 in discussing the beneficial effects of reducing the amount of organized school or leisure activities are much more convincing than would be a brief dogmatic statement. The brief historical review (pp. 448-9) of the effects of praise and blame in education conveys the correct impression that knowledge of a subject is not absolute but continually in flux.

The authors quote from a wide knowledge without committing themselves exclusively to the views of one school. To anyone wishing to study a subject this book will provide a useful and readable start with references to reviews as well as to original articles. Each chapter ends with questions for class-study and suggestions for visits.

This book should be required reading for anyone whose job is such that they are asked either in professional or social contacts to explain about growth, diet, thumb-sucking, 'telling lies,' backwardness in reading, stealing, or adolescent sexuality. Written 'in full appreciation of the fact that most college students will become parents and hence will need to understand children' it succeeds in supplying what their needs demand in a form from which they will easily profit.